Archives of Neurology and Psychiatry

VOLUME 47 APRIL 1942 NUMBER 4

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STUDIES ON THE CORPUS CALLOSUM

I. LATERALITY IN BEHAVIOR AND BILATERAL MOTOR ORGANIZATION IN MAN BEFORE AND AFTER SECTION OF THE CORPUS CALLOSUM

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The present paper proposes to describe possible relationships existing between laterality or sidedness in behavior and neural activity mediated by the corpus callosum, the main commissural fiber system between the two cerebral hemispheres. The experiments, based on observation of human subjects, are concerned with measurement of laterality before and after division of the fibers of the corpus callosum in patients with convulsions (Van Wagenen and Herren[1]).

The terms sidedness and laterality in behavior refer to a fundamental neurologic and psychologic aspect of bilateral motor coordination, for it is evident that the regulation of movement in all motor activity demands a leading role or preferential use of one side of the body over the other. The fact that one of a pair of bilaterally symmetric muscle groups plays such a leading or preferential role more or less permanently

This study was aided by grants furnished by the Ernest L. Woodward Fund and the John and Mary R. Markle Foundation.

The surgical operations on the patients described in this study were carried out by Dr. William P. Van Wagenen, of the Department of Surgery, Division of Neurosurgery, the University of Rochester School of Medicine and Dentistry, and Strong Memorial Hospital.

From the Laboratory of Psychology, the University of Rochester (Dr. Smith), and the Department of Medicine, the University of Rochester School of Medicine and Dentistry, and the Clinics of the Strong Memorial and Rochester Municipal Hospitals (Dr. Akelaitis).

Dr. William P. Van Wagenen made available the patients for this study, and Dr. Wilford A. Risteen contributed to the program of study.

1. Van Wagenen, W. P., and Herren, R. Y.: Surgical Division of Commissural Pathways in the Corpus Callosum: Relation to Spread of an Epileptic Attack, Arch. Neurol. & Psychiat. **44**:740 (Oct.) 1940.

in a majority of activities carried out by the organism has laid the basis for the acceptance of the psychologic concept of sidedness or laterality and its subordinate hypotheses, handedness, footedness, eyedness, etc. By implication, it is assumed that observations or test situations which reliably bring out the persistent characteristics of handedness, eyedness and footedness are valid measures of the psychologic aspects of laterality.

At present, the essential psychologic features of behavior laterality in a given person can be discussed with fair clarity in terms of quantified test results and case history, but the problems of the physiologic and anatomic bases of sidedness may be dealt with only by reference to speculative ideas or rational hypotheses based on selected psychologic facts. One widely accepted formulation of the anatomic and physiologic problem of sidedness is a modified concept of lateral cerebral dominance, a theory which originally developed in neurology as one explanation of the more significant role played by one hemisphere in the neural control of speech functions, complex perceptual processes and higher motor integrations. Modified to account for certain of the observed facts of laterality in behavior, the concept of lateral cerebral dominance (Orton,[2] Travis [3]) posits explicitly or implicitly the following conditions (fig. 1): 1. The structural antitropy of bilaterally symmetric muscle systems is correlated with an inherent functional antitropy, or mirrored action, of these systems in simultaneous or successive movements. 2. One cerebral hemisphere inherently controls muscular activity of one side of the body. 3. Integration of the two sides of the body is accomplished by the inhibitory action of one hemisphere (the dominant side) over the subordinate hemisphere, which inhibitory action is carried out through interhemispheral commissural systems. According to Liepmann [4] this inhibitory action is accomplished mainly via the fiber systems of the corpus callosum. 4. Lack of cerebral dominance is associated with ambilaterality, motor incoordination and speech defects or, especially, incoordination of muscle systems arranged near the midline of the body in which structural and functional antitropy is poorly developed or difficult to maintain, as in the case of the muscles of the larynx.

Physiologic observations have been made with reference to these ideas of sidedness. Using a test of paw preference in eating (Tsai and Maurer [5]), Peterson [6] observed that right pawedness in the rat may

2. Orton, S. T.: Reading, Writing, and Speech Problems in Children, New York, W. W. Norton & Company, Inc., 1937.

3. Travis, I. E.: Speech Pathology, New York, D. Appleton and Company, 1931.

4. Liepmann, H.: Die linke Hemisphäre und das Händeln, München. med. Wchnschr. **52**:2322 and 2375, 1905.

5. Tsai, L. S., and Maurer, S.: Right Handedness in Rats, Science **72**:436, 1930.

6. Peterson, G. M.: Mechanisms of Handedness in the Rat, Comparative Psychology Monographs, Baltimore, Johns Hopkins Press, 1934, vol. 9, no. 6.

be changed to left pawedness after lesions in the left frontal cortex, i.e., in the region roughly corresponding to the area controlling placing and hopping reactions. These results appear to be equivalent to the observation that lesions of the motor area in man cause shifts in the preferential use of the hands as a result of the paralysis of the preferred side. Kirk [7] and Herren and Lindsley [8] showed in experiments on the rat that perceptual orientation is not disturbed by lesions in the brain which

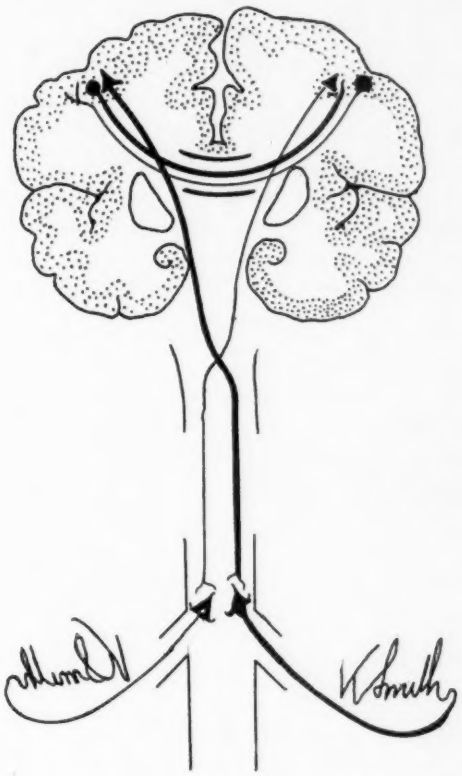

Fig. 1.—Diagrammatic sketch illustrating Orton's theory of sidedness and lateral cerebral dominance.

change the paw preference of the animal. In these studies, tests of visual orientation were made by means of a maze and by training rats

7. Kirk, S. A.: Hemispheric Cerebral Dominance and Hemispheric Equipotentiality, Comparative Psychology Monographs, Baltimore, Johns Hopkins Press, 1935, vol. 11, no. 5.

8. Herren, R. Y., and Lindsley, D. B.: A Note Concerning Cerebral Dominance in the Rat, J. Genet. Psychol. **47**:469, 1935.

in the discrimination of a visual pattern presented in its normal and mirrored position. According to these investigators, the view of Orton [9] would predict that changes in laterality would be associated with shifts in visual orientation.

Reported association of ambilaterality or shifts in handedness with different types of behavior dysfunction has been taken as evidence for the central dominance theory of sidedness. It is assumed that, since central dominance is basic to both sidedness and motor coordination, absence of sidedness should be associated with generalized neurologic and psychologic dysfunction. Ambilaterality has been alleged to be increased in persons with speech disorders (Bryngelson,[10] Jasper,[11] Johnson and Duke,[12] Travis,[3] Travis and Johnson [13]), mental deficiency (Dart [14]), psychoses and psychopathic conditions (Chandler [15]), behavior problems (Jasper and Raney [16]), school deficiency (Oates [17]) and reading disability (Orton,[2] Dearborn [18]). The nature of the relation between ambilaterality and these different behavior disorders, it must be admitted, is highly problematic at present. In connection with observations of this sort, however, Travis and Knott [19] and Lindsley [20]

9. Orton, S. T.: Word Blindness in Children, Arch. Neurol. & Psychiat. **14**: 581 (Nov.) 1925.

10. Bryngelson, B.: Sidedness as an Etiological Factor in Stuttering, J. Genet. Psychol. **47**:204, 1935.

11. Jasper, H. H.: A Laboratory Study of Diagnostic Indices of Bilateral Neuromuscular Organization in Stutterers and Normal Speakers, Psychological Monographs, Columbus, Ohio, Psychological Review Company, 1932, vol. 43, no. 1.

12. Johnson, W., and Duke, L.: Changes in Handedness Associated with Onset or Disappearance of Stuttering: Sixteen Cases, J. Exper. Educ. **4**:112, 1935.

13. Travis, L. E., and Johnson, W.: Stuttering and the Concept of Handedness, Psychol. Rev. **41**:534, 1934.

14. Dart, C.: The Hand, Eye, and Foot Preference of Two Hundred Mentally Subnormal Subjects and Two Hundred Subjects of Normal or Superior Intelligence, Psychol. Bull. **31**:593, 1934.

15. Chandler, C. M.: Hand, Eye, and Foot Preference of Two Hundred Psychotic Patients and Two Hundred Students, Psychol. Bull. **31**:593, 1934.

16. Jasper, H. H., and Raney, E.: The Physiology of Lateral Cerebral Dominance, Psychol. Bull. **34**:151, 1937.

17. Oates, D. W.: Left-Handedness in Relation to Speech Defects, Intelligence and Achievement, Forum Educ. **7**:91, 1929.

18. Dearborn, W. F.: Structural Factors Which Condition Special Ability in Reading, Proc. Am. A. Ment. Deficiency **38**:268, 1933.

19. Travis, L. E., and Knott, J. R.: Bilaterally Recorded Potentials from Normal Speakers and Stutterers, J. Speech Disorders **2**:239, 1937.

20. Lindsley, D. B.: Bilateral Differences in Brain Potentials from the Two Cerebral Hemispheres in Relation to Laterality and Stuttering, J. Exper. Psychol. **26**:211, 1940.

attempted to discern the differences in synchronism and blocking of the alpha rhythm of the cortex between stutterers and normal speakers.

Those who believe that central dominance is the basis for sidedness assume generally that the central dominance is inherent. Using a special test of central dominance, based on the appearance of the phi phenomenon in nonhomonymous retinal quadrants with different visual fixations, Raney [21] stated that opposed sidedness is more frequently found than correlated sidedness in identical twins. Mirror twins, i.e., identical twins having mirrored handedness, show mirrored cerebral dominance according to this special test. There were no clear differences between electroencephalograms of identical twins having mirrored "cerebral dominance" (Raney [22]).

At present the view of lateral cerebral dominance as a basis for behavior laterality is opposed by no other systematic belief, except the view that sidedness is learned and is specific for different behavior patterns. It is impossible to organize logically a significant number of observed facts of laterality under this hypothesis.

OPERATION AND METHOD

The present experiment, which is concerned with the effects of partial and complete section of the corpus callosum on motor organization, has afforded a means of evaluating directly the general concept of cerebral dominance, inasmuch as the major portion of the interhemispheral fibers passes through the corpus callosum. The anterior and posterior commissures contribute at most only a very small number of fibers to the neopallium.

Sixteen patients, 8 with complete and 8 with partial section of the corpus callosum, were made available for study. Two additional patients with neurologic conditions of significance to this investigation were also studied. All of these patients were subject to both grand mal and petit mal attacks. In table 1 are described the preoperative neurologic condition, the nature of the operation and the postoperative recovery of each patient observed. The patients have been classified into three groups: those with complete section of the corpus callosum, those with partial section and those displaying other neurologic conditions. Extent of section of the corpus callosum has been indicated according to the judgment of the surgeon at the time of operation. The method of retraction of the cerebral hemispheres permitted clear visualization of the operative field. The basis of this surgical procedure has been described by Van Wagenen and Herren.[1]

Among a battery of laterality measures which were used with these patients was included a performance test which has been developed from several laterality

21. Raney, E. T.: Reversed Lateral Dominance in Identical Twins, J. Exper. Psychol. **23**:304, 1938.

22. Raney, E. T.: Brain Potentials and Lateral Dominance in Identical Twins, J. Exper. Psychol. **24**:21, 1939.

TABLE 1.—*Clinical Data on Sixteen Patients with Complete or Partial Section of the Corpus Callosum and on Two Patients with an Associated Neurologic Lesion*

Case	Patient, Sex, Age	Preoperative Status	Operation	Postoperative Status
		A. Complete Section of the Corpus Callosum		
1	E. C. Male 12 years	Cerebral atrophy; athetoid movements; cerebral involvement	2/19/40: complete section of corpus callosum; right craniotomy	Right-sided paralysis, which partly cleared
2	C. S. Female 16 years	Residua of left hemiplegia	1/23/40: complete section of corpus callosum; right craniotomy	Temporary accentuation of hemiplegic signs, with sensory changes
3	G. E. Male 35 years	Cleared left fronto-parietal abscess; right midthigh amputation; stuttering and motor aphasic signs	5/17/40: complete section of corpus callosum; right craniotomy	Recovery uneventful; no sensory or motor signs
4	F. O'B. Male 27 years	Visual agnosia in left homonymous field	11/3/39: complete section of corpus callosum; right craniotomy	Recovery uneventful
5	F. R. Female 26 years	Left Erb's birth palsy; absence of left biceps reflex	2/23/39: division of body of corpus callosum; section of left fornix; 5/25/39: section completed; right craniotomy in both operations	Left hemiparesis after first operation; cleared subsequently
6	E. B. Female 24 years	Mental deterioration	3/18/39: Section of body and posterior half of genu; 4/24/39: rest of corpus callosum sectioned; right craniotomies	Recovery uneventful
7	E. K. Female 30 years	Cerebral scar in right parieto-occipital region; aura of numbness on left side	11/21/39: complete section of corpus callosum; right fornix divided; right craniotomy	Catatonic state, with mutism of two weeks' duration, which cleared
8	G. B. Male 14 years	Left hemiplegia with athetosis	5/19/39: complete section of corpus callosum; right craniotomy; 11/28/39: right frontal lobectomy	Unchanged
		B. Partial Section of the Corpus Callosum		
9	E. H. Male 52 years	Some cerebral atrophy; organic defects indicating cerebral involvement; Pick's disease	4/6/40: complete section of corpus callosum except for a few fibers at tip of the splenium; right craniotomy	Transient left paresis following jacksonian attacks; right hemiplegia with motor aphasia cleared completely
10	C. N. Female 36 years	Psychotic equivalents	4/4/39: section of body and genu of the corpus callosum; right craniotomy	Unchanged
11	E. V. B. Female 28 years	Astrocytoma with resection of anterior two thirds of right temporal lobe in 1937	4/21/39: division of entire genu and body of corpus callosum; right craniotomy	Recovery uneventful
12	W. S. Male 28 years	Nothing significant	2/22/39: division of body and genu of corpus callosum for distance of 5 cm.; 5/4/39: section of rest of corpus callosum except for 1 cm. at tip of splenium; left fornix cut; right craniotomies	Temporary paresis of left arm; retrograde thrombosis of vein in right frontal lobe
13	F. P. Male 17 years	Obsessions, compulsions and assaultive behavior; suicidal intent	3/25/40: complete section of corpus callosum except for 1 cm. at tip of splenium; left craniotomy	Recovery rapid and uneventful
14	S. L. Male 21 years	Some cerebral atrophy	1/8/40: section of 5 cm. of the body and genu of the corpus callosum; right craniotomy	Recovery rapid and uneventful
15	M. L. P. Female 10 years	Residua of right hemiplegia dating from 3 yr. of age	3/29/40: complete section of corpus callosum except for 0.5 cm. at tip of splenium; division of left fornix; right craniotomy	Hemiplegic residua remain, with grasp reflex in right hand

TABLE 1.—*Clinical Data on Sixteen Patients with Complete or Partial Section of the Corpus Callosum and on Two Patients with an Associated Neurologic Lesion—Continued*

Case	Patient, Sex, Age	Preoperative Status	Operation	Postoperative Status
16	W. M. Female 18 years	Nothing significant	11/13/40: complete section of corpus callosum except for few fibers at tip of splenium; right craniotomy	Recovery uneventful
		C. Associated Neurologic Conditions		
17	E. R. Male 28 years	Agenesis of the corpus callosum	5/8/40: section of mass of tissue 2 cm. in diameter lying between frontal lobes; biopsy indicated invasion of right cortex into left hemisphere through a defect in the falx	Recovery uneventful
18	L. C. Male 16 years	Compound fracture in left occipital region in 1936	7/26/39: left occipital lobectomy; later evacuation of a clot in the cavity of the resected lobe	Continuation of attacks

questionnaires, especially that used by Jasper.[11] In table 2 are described the different items of the performance test, classified according to the types of motor adjustment involved. In all, 97 distinct items were used in the test, but 3 tests of eyedness and 5 of footedness were repeated three and two times, respectively, to give a total of 108 items. It should be emphasized that the items of the test were performed by the patients, either with actual instruments or with substitute devices.

This performance test was presented to 8 of the patients from three to seven days prior to the operation. To 1 (patient 16) it was possible to give the test twice before operation. Postoperative tests were ordinarily given to the patients when they had recovered sufficiently to be able to move about normally. In the cases in which motor deficiency appeared postoperatively (cases 1, 5, 9 and 12) tests were postponed for some months after operation. When the tests were finally made the motor signs had completely disappeared in case 9 and had been greatly reduced in the other 3 cases. In 3 cases (4, 13 and 15) it was possible to carry out more than a single postoperative observation.

RESULTS

The results of the experiment may be discussed with reference to the following main topics: (1) the initial effects of the operation on representative motor skills, and (2) laterality in behavior after section of the corpus callosum as indicated by the performance test.

1. *Initial Effects of the Operation on Representative Motor Skills.*—Most of the patients observed in this study were examined carefully soon after recovery from the anesthesia, or as soon as they were able to understand spoken words. The surgeons in charge reported that some of the patients displayed difficulty in distinguishing between the right and the left hand immediately after recovery from the anesthesia. We can confirm this defect in only 3 cases (1, 2 and 9). It is to be

noted that in all these 3 cases the patient displayed evidence of cerebral disorder after operation which could not be attributed entirely to sectioning of the corpus callosum.

TABLE 2.—*Performance Test Used in Measuring Laterality of Patients with Section of the Corpus Callosum*

Eyedness	Eye-Hand Coordination, Bimanual	Eye-Hand Coordination, Unimanual
1. Aim a gun	1. Hold a bat	1. Use a key
2. Sighting	2. Hold a club	2. Carry a cup
3. Sighting	3. Swing a bat	3. Drink from a glass
4. Sighting	4. Use a billiard cue	4. Turn a doorknob
5. Convergence	5. Deal cards	5. Pull out a drawer
6. Convergence	6. Hold a gun	6. Hang up a hat
7. Convergence	7. Use a needle	7. Pick up a small object
8. Monoptoscope	8. Thread a needle	8. Reach to a high shelf
9. Monoptoscope	9. Use scissors	9. Turn a top
10. Monoptoscope	10. Use a can opener	10. Throw a ball
		11. Swing a tennis racket
		12. Affix a stamp

Tool Using, Bimanual	Tool Using, Unimanual	Manipulation, Bimanual
1. Use a hoe	1. Hold a fork	1. Wind a watch
2. Use a rake	2. Use a razor	2. Shuffle cards
3. Use a pitchfork	3. Use a saw	3. Fill a pen
4. Use a shovel	4. Use a hammer	4. Tear open an envelope
5. Hold a broom	5. Use a screw driver	5. Wash a dish
6. Hold a spade	6. Use a wrench	6. Wash the hands
7. Hold an ax	7. Crank an instrument	7. Tie a tie
8. Sharpen pencil	8. Turn a bolt	8. Handle money
9. Cut meat	9. Hold a telephone	9. Tie a shoestring
10. Turn an egg beater	10. Stir with a rod	10. Uncork a bottle
		11. Clasp hands
		12. Fill an envelope

Manipulation, Unimanual	Body Orientation
1. Turn pages of a book	1. Direction of sweeping
2. Turn on a lamp	2. Side slept on
3. Use a salt shaker	3. Put on a coat
4. Comb the hair	4. Pick up right shoe
5. Strop a razor	5. Pick up left shoe
6. Use a powder puff	6. Take off shoes
7. Use a toothbrush	7. Put on shoes
8. Light a match	8. Put on stockings
9. Hold a cigaret	9. Take off stockings
10. Use a dust cloth	10. Rise from a sitting position
11. Turn a dial	11. Direction of turning
12. Hold a book	12. Listen to sounds
13. Take objects from a box	

Footedness	Writing
1. Kick an object	1. Write name
2. Kick an object	2. Draw pictures
3. Step on a spade	3. Write figures
4. Step on a spade	4. Erase
5. Step forward in falling	5. Mirror writing
6. Step forward, etc.	6. Critical angle writing
7. Jump	7. Bimanual writing
8. Jump	8. Bimanual drawing
9. Push with one foot	9. Bimanual figures
10. Push with one foot	10. Writing upside down

Samples of writing were obtained from the patients shortly after operation. Patient 13 (with complete section of the corpus callosum except for 1 cm. of the splenium) wrote on request with either hand the day after operation. In figure 2 *A* samples of his writing at this time, as well as samples secured twenty days after operation, are pre-

Fig. 2.—Samples of writing and drawing by 3 patients shortly after section of the corpus callosum.

sented in comparison with his preoperative writing. Drawings made with each hand on the third postoperative day are also shown. Patient 16, who had the corpus callosum completely sectioned except for a few fibers at the tip of the splenium, exhibited some forced innervation of the left hand for about a week after operation. Nevertheless, she was able to write with either hand two days after operation. Samples of her handwriting two and six days after operation are shown in figure *2 B*. Also included in figure *2 C* are samples of writing of patient 3, in whom the corpus callosum was completely sectioned. Two days prior to the operation this patient was requested to write his name with both the right and the left hand forward upright, mirrored upright, forward upside down and mirrored upside down. Eight comparable samples of writing were then secured postoperatively. As shown in the figure, the patient was as skilful after the operation as before in producing the various types of writing. The same peculiarities of movement appear in corresponding samples of preoperative and postoperative writing, as, for example, in samples 1 and 5.

There was no indication in the patients in whom recovery from the operation was not complicated by signs of organic lesion to the brain in addition to section of the corpus callosum that common tasks of eating, dressing, locomotion, etc., were seriously disturbed by the operation, except possibly for some slowing of the speed of reaction.

Few, if any, speech defects were noted in these patients after section of the callosum. Patient 3, who stuttered as a child and had had a recurrence of this disturbance along with mild aphasic signs after evacuation of an abscess of the left frontoparietal portion of the brain in 1937, displayed no exaggeration of the stutter after section of the corpus callosum, nor did his speech improve while he was under observation during convalescence. Patient 13, who displayed preoperatively infrequent speech blocks during emotional excitement, gave no indication that his speech habits were changed subsequent to operation. Patient 7, with complete section of the corpus callosum, portrayed a type of catatonic mutism for weeks after the operation, from which she recovered completely.

Certain complex motor skills, demanding a high degree of bilateral motor integration, were within the behavior repertoire of some of the subjects prior to operation. Patient 11, who had been an accomplished typist and a secretary by vocation, was able to type German passages within a relatively short time (two months) after the operation. Patient 5, with complete section of the corpus callosum, could type German passages by the touch system after operation. Three weeks after operation patient 13 demonstrated his ability to tap dance, at which he was fairly proficient. Patients 5 and 12 suffered some inability to play the piano and steel guitar respectively after operation, but it is to be noted

that in both these patients there was clear evidence of transient disturbance of the upper motor neuron after operation. The case of patient 12 was complicated by retrograde thrombosis of a ligated vein in the right frontal lobe. Patient 5 regained in a year her ability to play the piano as efficiently as before operation. Patient 12 was never able to manipulate the string board with his left hand adequately to render a melody, although he placed the fingers of the left hand correctly when blindfolded to produce various chords on request.

The aforementioned observations indicate clearly that disturbances of unilateral and bilateral motor skills occur infrequently after section of the corpus callosum. Those cases in which such disturbances were noted were complicated by the presence of pathologic conditions not directly dependent on the callosal section.

Most of the patients experienced no mental confusion in connection with the status of their laterality subsequent to the operation. In a few patients, however, there appeared instances of dissociation of opposed movement systems. Patient 5 exhibited a transient disorder in which she performed curious antagonistic reactions, such as attempting to put on an article of clothing with the right hand and pulling it off with the left. Patient 4 displayed persistent movement antagonisms for a short period after the operation, such as picking up a deck of cards, putting it down and picking it up. Other than those in the cases just cited, the patients experienced no serious disturbances in their ability to coordinate the two sides of the body in the performance of tasks. Patient 14 was often undecided, when asked to perform simple tasks, as to the role each hand should play. However, he performed the tasks with no motor difficulty and usually carried them out in the same manner as he had preoperatively. Memory for the preoperative method of performance of different tasks was generally unimpaired, although some temporary changes in the nature of laterality in such performance did occur, as will be shown later. Idiosyncrasies of movement which characterized the motor organization of some of the patients reappeared subsequent to operation. For example, nervous habits of arranging the clothes, stroking the face or hair and general postural habits were marked by the same individual peculiarities postoperatively as preoperatively in the patients in whom no debilitating condition was present after the operation.

2. *Laterality in Behavior After Section of the Corpus Callosum.*—Figure 3 illustrates the quantitative methods which have been utilized in the present study in describing the laterality status of the patient before and after operation. The 10 different items named at the top of the graph represent the psychologic aspects of laterality which were incorporated in the performance test. A quantitative index of laterality for these different aspects of motor organization is expressed as a

percentage value. The percentage of right or left laterality in each case is equal to the number of performances executed by the dominant side minus those performed by the nondominant side divided by the total number of tasks in a given group. For example, for a subject predominantly right sided in tasks involving bimanual eye-hand coordination, the index for this type of activity would be the number of tasks performed by the right side minus those performed by the left side divided by 10, the total number of tasks in this group. Tasks performed in an ambilateral manner, or likely to be performed by one side as well as the other, are not considered in calculating the indexes. The indexes

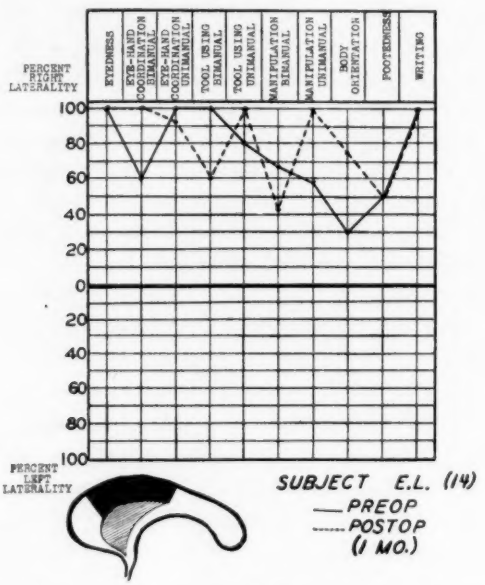

Fig. 3.—Laterality profiles in case 14 before and after section of the corpus callosum.

calculated may be said to represent the percentage deviation from perfect ambilaterality.

Figure 3 shows a laterality profile, plotted in terms of indexes of the sort just described, for patient 14, in whom the body and part of the genu of the corpus callosum were divided. The percentage of right laterality in the various groups of tasks is given in the upper half of the graph; the percentage of left laterality, in the lower half. The midline thus represents ambilaterality. The heavy line graph represents the nature of motor organization of the patient prior to operation; the dotted line graph, that subsequent to operation. The figure drawn below the laterality profile indicates the extent of the section of the

corpus callosum. In this case, tests made one month subsequent to operation indicated that the postoperative motor organization differed somewhat from that found prior to section of the commissure. Aspects of motor performance affected most were bimanual eye-hand coordination, bimanual tool using, unimanual manipulation and body orientation. All of these functions showed a shift of at least 40 per cent in terms of the indexes used. This degree of shift represents a reversal in laterality for at least two tasks in a given type of performance, a change much greater than that which can be expected to occur with retests of a normal subject, as will be seen later. It is to be noted that eyedness, unimanual eye-hand coordination, unimanual tool using, bimanual manipulation, footedness and writing were not significantly changed in this patient after operation.

Figure 4 presents results for 4 patients (9, 13, 15 and 16) in whom the corpus callosum was almost completely sectioned except for a small part of the splenium. These 4 patients are interesting in that 2 of them (13 and 15) had left-sided characteristics. Patient 9 showed significant shifts in laterality in unimanual eye-hand coordination, body orientation and footedness. This man passed through a stormy convalescence, during which he was confused and could not use his left hand in identifying objects, but when tested four months after operation he showed only limited shifts in motor integration. The other right-handed person of this group (patient 16) was tested twice before operation, with an interval of approximately two months between tests. It may be said that these two preoperative tests showed no significant differences. At most, there was shift in laterality of only 1 item (20 per cent in case this was a reversal in laterality) in any one group of performances. Different examiners administered the tests at the two different times. When tested three weeks after operation this patient displayed no significant changes in laterality. One preoperative and two postoperative observations were made on patient 13. This partly ambidextrous boy displayed a lateral organization of motor performance that is a lesson in itself to those who believe in the unitary character of sidedness. Before operation this patient was moderately right sided in all performances but bimanual tool using and body orientation. Postoperatively marked shifts occurred in all aspects of his motor organization except eyedness and writing. These changes were especially marked in the first postoperative test in unimanual eye-hand coordination, unimanual and bimanual tool using and manipulation and footedness. On the second postoperative test the shifts were less marked and the laterality profile more nearly approximated the preoperative level. Two postoperative tests were also obtained on patient 15, a young girl possessed of the residua of right hemiplegia of seven years' standing. This patient was reported to have been right handed as a child, but

after the onset of the hemiplegia, with temporary aphasia, following a fall, the left hand was predominantly used. Nevertheless, in bimanual tool using this patient was still right handed to some extent. One month

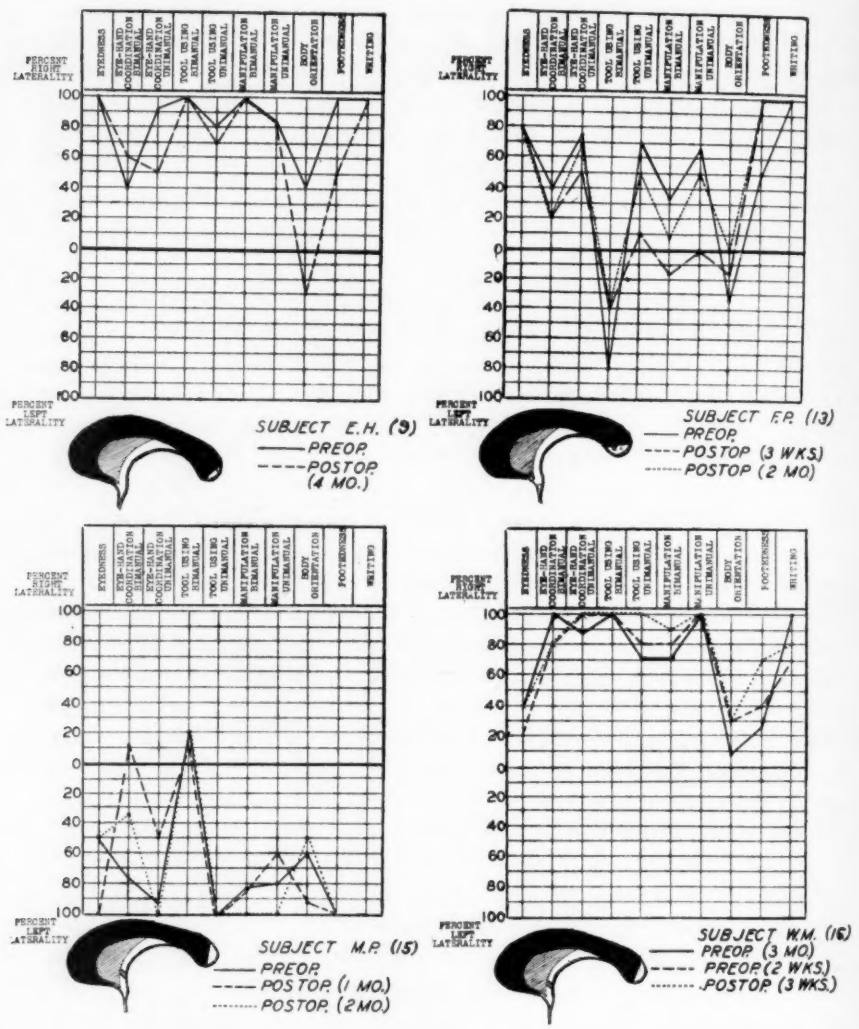

Fig. 4.—Laterality profiles of 4 patients before and after section of the corpus callosum.

after the operation the motor organization of this patient was like that found preoperatively, except in tasks involving unimanual and bimanual eye-hand coordination and body orientation. Again, as with patient 13, a second postoperative test showed readjustment of the motor organiza-

tion toward the preoperative status. Comparison of the data on these 4 patients with comparable lesions of the corpus callosum seems to indicate that the 2 patients showing some degree of ambilaterality or

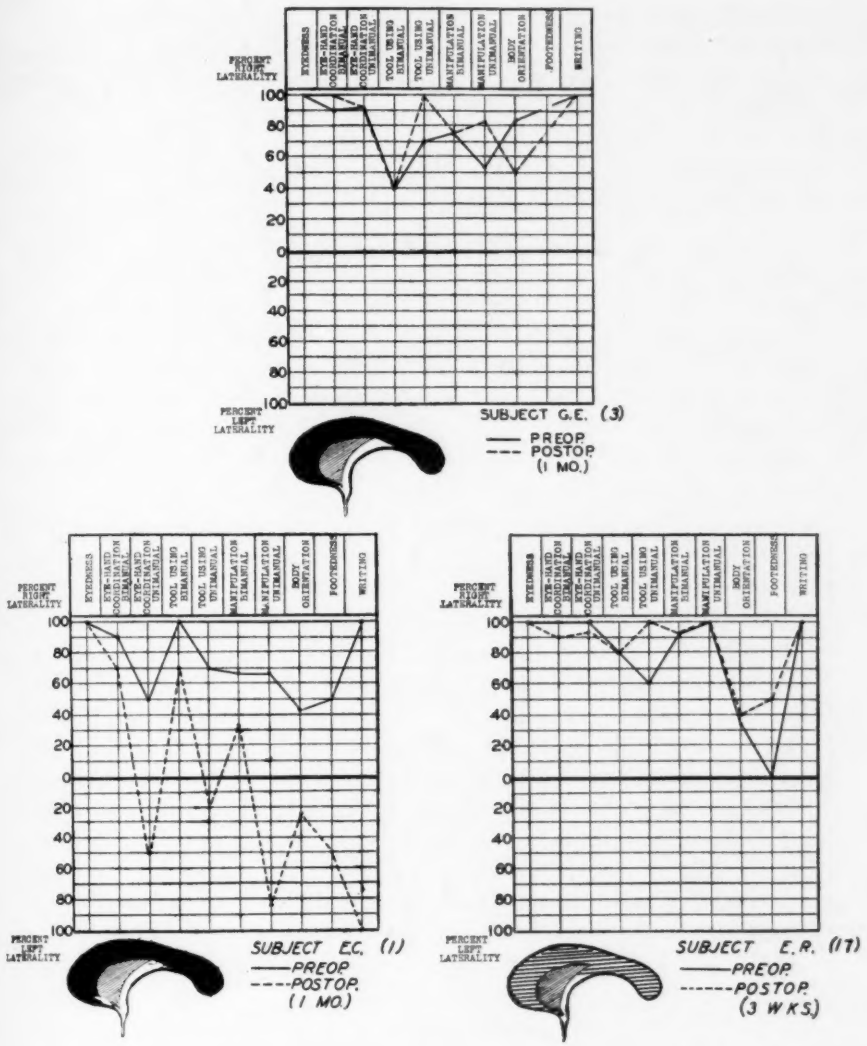

Fig. 5.—Laterality profiles of 3 patients, 2 with complete section of the corpus callosum (cases 1 and 3) and 1 with agenesis of the corpus callosum.

left handedness were more significantly affected by the operation than those displaying marked right laterality.

In figure 5 are shown laterality profiles for 2 patients (3 and 1) in whom the corpus callosum was completely sectioned and for a third

(patient 17) having agenesis of the corpus callosum. Subsequent to operation patient 3, who was strongly right sided, displayed changes in laterality in relation to unimanual tool using, unimanual manipulation and body orientation, in all three of which the shift in laterality could be said to be important. The right leg of this patient had been amputated; hence measures of testing footedness were not taken. In patient 1, who was also right sided, moderate paralysis of the right side associated with sensory changes developed approximately two weeks after operation. This condition appeared after a series of radical seizures which began soon after operation and continued for the time the patient was under observation. Testing of his laterality status one month after operation revealed shifts in sidedness which could be expected on the basis of the marked deficiencies in motor capacity on the right side. It is notable that in the case of tasks involving use of the hands unimanual performances were more radically changed than bimanual performances. This boy could no longer write with his right hand. His footedness and body orientation were reversed in part, but eyedness was not altered.

The changes in laterality in the case last mentioned serve to illustrate the modification in motor organization occurring as a result of involvement of the pyramidal motor system on one side, for it is evident that the paralysis in this case was the result of organic disturbance in the upper motor neurons.

Patient 17 came into the hospital with a previous diagnosis of agenesis of the corpus callosum based on the encephalographic pattern. This diagnosis was subsequently confirmed. Section of a mass of tissue 1 cm. in diameter lying between the frontal poles, which was later shown histologically to be herniation of cortical tissue of the right hemisphere through a defect in the falx, was carried out in this case. Tests prior to and two weeks subsequent to operation indicated no marked instability of laterality as a result of the operation. Some changes in laterality occurred after operation in unimanual tool using and footedness. Two years prior to these observations the laterality of this patient was measured by questionnaire by Dr. James D. Page. The results of this investigation, which was not as complete as observations made in the present study, agree, however, in almost every detail with the postoperative performances shown in figure 5. This man, exhibiting partial or complete absence of the commissural fibers of the corpus callosum, became decidedly right sided, with some degree of skill as a butcher.

An additional patient (case 2) with complete section of the corpus callosum was observed both preoperatively and postoperatively. Because of left hemiplegia which existed preoperatively, and which became exaggerated subsequent to operation, the tests on this patient were

necessarily incomplete. For that reason, her laterality profile has not been presented. Suffice it to say that there were no changes in laterality in this subject except for an increase in the degree to which the right

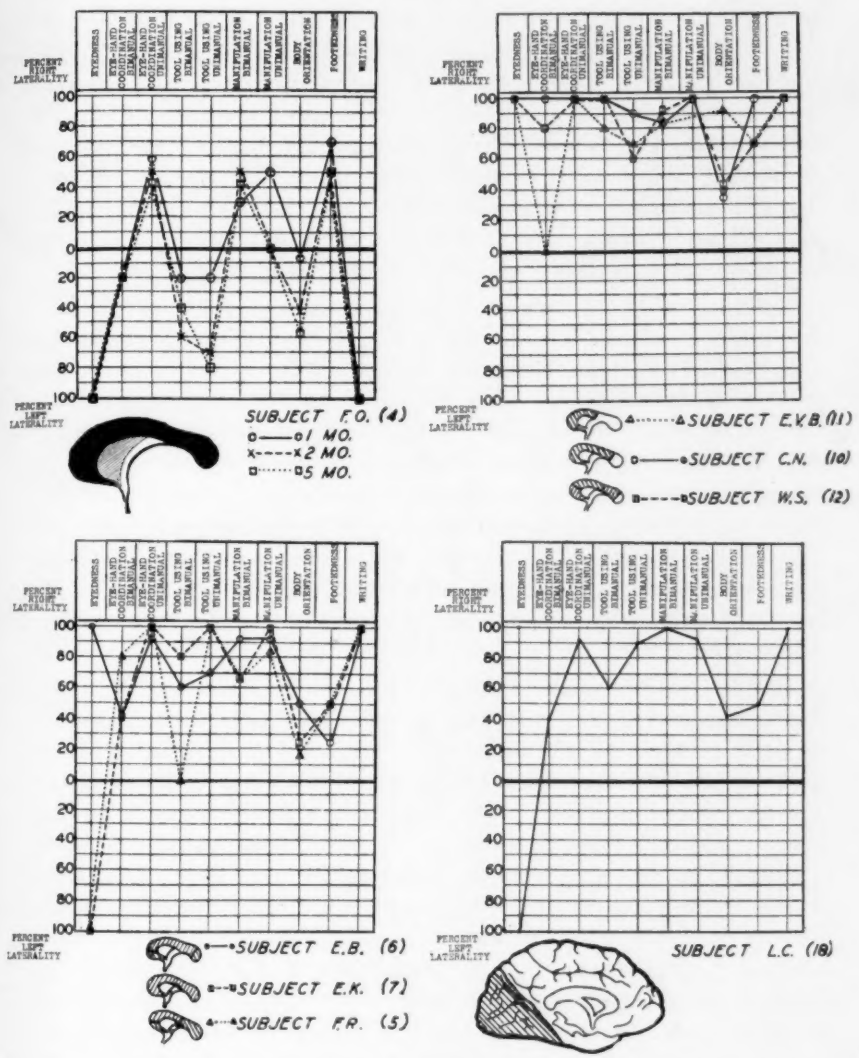

Fig. 6.—Postoperative laterality profiles of 7 patients with section of the corpus callosum and 1 with left occipital lobectomy.

hand had to be used in bimanual performances, since the left hand was almost completely useless.

Figure 6 summarizes results for 8 patients tested only postoperatively. At the upper left in the figure are shown three postoperative

profiles of a predominantly left-handed man in whom the corpus callosum was completely sectioned. In the first series of tests, one month after operation, this patient gave evidence of a high degree of ambilaterality, except for behavior related to eyedness and writing. Two months after operation some changes in laterality with respect to unimanual and bimanual tool using, unimanual manipulation and footedness had occurred. On a subsequent test the laterality profile remained much the same, having no significant differences from that in the second postoperative test. The extent of change found between the first and the second postoperative observation in this predominantly left-sided patient is much the same as that found between tests made before and after operation in patients 13 and 15, who also displayed significant degrees of left sidedness.

The upper right graph in figure 6 presents laterality profiles of 3 patients (11, 10 and 12) in whom the fibers of the corpus callosum were partly sectioned. The extent of the section in each case is indicated in the drawing below the graph, in which areas with lines directed toward the lower left indicate the extent of section in a first stage of the operation and those with lines directed toward the lower right the degree of section in a second stage. All 3 subjects represented in this graph had a history of strong right handedness since early childhood. Their postoperative profiles showed that generally this right sidedness has been maintained after operation. In only 1 instance does the performance seem to be ambilateral, in bimanual eye-hand coordination of patient 11.

Similar results are presented in the lower left graph for 3 patients with complete section of the corpus callosum. Two of these patients also had histories of decidedly right laterality since early childhood. After operation 2 (patients 5 and 7) were left eyed, 1 (patient 5) gave evidence of ambidextrous performance in bimanual tool using and all 3 displayed weak right sidedness in body orientation and footedness. Otherwise, in all 3 patients strongly right-sided motor organization persisted. It is worthy of note that the pattern of laterality, except for variations in eyedness, was similar in this group of patients to that in the corresponding group with partial section of the callosum. Unimanual performances generally displayed a greater degree of right sidedness than did bimanual activities, while body orientation and footedness showed still less marked sidedness. This is also true in normal persons.

The observations made on the 6 patients just discussed were carried out during a postoperative period of some eighteen months. It seems likely, therefore, that in right-handed persons, at least, there is no gradual disintegration of sidedness toward ambilaterality after section of the commissural pathways of the corpus callosum. None of the

observations made here indicates that eyedness may be shifted by lesions of the corpus callosum. That reversal of eyedness may occur after removal of regions of the cerebral cortex is shown in case 18, in which the patient was known to have possessed originally a condition of right eyedness, coupled with strong right sidedness in other aspects of motor organization. Subsequent to an accident which necessitated a left occipital lobectomy, this patient still gave evidence of fairly well defined right handedness, except in bimanual eye-hand coordinations, but his eyedness was reversed to the left side (lower right profile in figure 6). This evidence suggests that eyedness, like handedness, may have either direct or indirect functional relation to paired centers of the cerebral cortex.

With the foregoing case descriptions in mind, it seems profitable at this point to inquire into systematic changes, occurring before and after section of the corpus callosum, which may be discerned by examination of combined data for several subjects. In discussing these data it should be noted that the limited number of cases available precludes the possibility of extensive statistical treatment. Nevertheless, a number of observable consistencies are worthy of mention.

It has been possible to obtain complete preoperative and postoperative observations on 6 patients in whom no serious postoperative motor disability occurred to hinder the testing of motor organization. In patient 14 the body and posterior half of the genu of the corpus callosum were sectioned; in patients 9, 13, 15 and 16 all the fibers except the posterior ones in the splenium were cut, and in patient 3 the entire corpus callosum was divided.

Table 3 summarizes the changes which occurred postoperatively in these 6 patients. The numbers appearing in this table represent percentage differences between the preoperative and the postoperative laterality status, as calculated by the method described previously. All differences given are calculated in terms of the last preoperative test made before operation and the first postoperative test carried out after the corpus callosum had been sectioned. Plus signs in the table indicate that the change in laterality is in the direction of increased dominance of the preoperatively determined dominant side of the body; minus signs, that the change is in the direction of ambidexterity or reversal of dominance. The table shows that writing habits and eyedness remained unchanged in all but 2 of the 6 subjects while other motor adjustments showed marked shifts in laterality. The three columns at the extreme right of the table show mean percentage increase, mean percentage decrease and mean total percentage change in laterality for each of the 6 patients. The mean increase in laterality for patient 3, for example, is calculated by taking the sum of all the increases shown (10+, 30+, 25+) and dividing it by the number of performance

groups, 10. The three rows at the bottom of the table show mean percentage increase and decrease and mean total percentage change for each of the 10 performance groups. Three in the group of 6 patients showed greater mean increase than decrease, while 3 showed greater mean decrease. However, of the 10 performance groups, 6 showed greater decrease, 3 showed greater increase and in 1 the increase and decrease figures were equal. The combined mean increase is 7.7 per cent and the mean decrease 11.9 per cent. This difference, while not statistically significant, indicates a tendency toward decreased laterality, i.e., changes in the direction of ambilaterality or reversed laterality, after section of the corpus callosum.

TABLE 3.—*Percentage Change in Laterality Following Section of the Corpus Callosum*

Case No.	Eyedness	Bimanual Eye-Hand Coordination	Unimanual Eye-Hand Coordination	Bimanual Tool Using	Unimanual Tool Using	Bimanual Manipulation	Unimanual Manipulation	Body Orientation	Footedness	Writing	Mean Increase	Mean Decrease	Mean Total Change
3	0	10+	0	0	30+	0	25+	33—	....	0	6.5	3.3	9.8
9	0	20+	42—	0	10—	0	0	72—	50—	0	2.0	17.4	19.4
13	0	20—	25—	40—	60—	50—	67—	17—	50+	0	5.0	27.9	32.9
14	0	40+	8—	40—	20+	25—	42+	50+	0	0	15.2	7.3	22.5
15	50+	86—	42—	10—	0	2+	20—	32+	0	0	8.4	15.8	24.2
16	20+	0	0	0	20+	10+	0	0	30+	10+	9.0	0.0	9.0
Mean increase	11.7	11.7	0.0	0.0	11.7	2.0	11.2	13.7	13.3	1.7	7.7		
Mean decrease	0.0	17.7	19.5	15.0	11.7	12.5	14.5	20.3	8.3	0.0	...	11.0	
Mean total change	11.7	29.4	19.5	15—	23.4	14.5	25.7	34.0	21.6	1.7	...	....	19.6

Of the 6 patients represented in table 3, patients 3, 9, 14 and 16 were predominantly right sided, patient 13 was ambilateral and patient 15 was definitely left sided. It is to be noted at this point, in addition, that patient 13 had a left craniotomy and patient 15 a right craniotomy. Both patients were shifted in handedness as children, patient 13 from left to right, patient 15 from right to left. It is interesting to note that the ambilateral and left-sided patients showed greater total changes in laterality after the operation than did any of the right-sided patients. In this connection, the test results for patient 4, another left-sided person, are relevant. On this patient no preoperative tests were obtained, but it was possible to test the patient three times postoperatively at intervals of approximately one month. The second and third postoperative profiles are very similar (fig. 6) and vary at several points from the first postoperative profile. We have assumed that the second profile represents roughly the preoperative laterality status of the

patient. On this basis we may compute the postoperative changes represented in the first test made and find that the patient shows a mean increase in laterality of 9.2 per cent and a mean decrease of 12.7 per cent, or a total mean change of 21.9 per cent. This high percentage of change is greater than the change shown by 3 of the right-sided patients in table 3 and is practically equivalent to the change shown by the fourth, patient 14. The results seem to indicate that right-sided persons in general show less disturbance in laterality as a result of section of the corpus callosum than do left-sided or ambilateral persons. The differences between right-sided and left-sided persons in this respect are summarized in table 4, which combines data on 4 right-sided patients (3, 9, 14 and 16) and 3 left-sided or ambilateral patients (4, 13 and 15). It will be seen that the mean total change is much greater for the latter group. Table 4 also shows that whereas for right-sided patients the mean percentage increase and the mean percentage decrease after the operation were about equal, for

TABLE 4.—*Effect of Dominance on Postoperative Shifts of Laterality*

Dominance	Mean Percentage Increase	Mean Percentage Decrease	Mean Total Percentage Change
Right sided	8.2	7.0	15.2
Left-sided and ambilateral	7.5	18.8	26.3

the left-sided and the ambilateral patients the mean percentage decrease was much greater than the mean percentage increase. That is, in left-sided persons the greater number of postoperative shifts are in the direction of right sidedness.

It should be emphasized again that, in general, postoperative shifts in laterality were only temporary. Within two or three months after the operation the patients approximated their preoperative laterality status.

SUMMARY AND CONCLUSIONS

It is definitely appreciated that no final conclusion concerning the role of the corpus callosum in laterality in behavior can be reached on the basis of investigation of patients over a postoperative period of only eighteen months at most. There is always the possibility that the subsequent history of these persons may show changes in laterality entirely at variance with observations made up to the present time. We propose to continue examination of the patients described here, patients with partial and complete section of the corpus callosum, for an indeterminate period, or until it is clearly evident that further study is without significance.

1. *Disturbances in Motility After Section of the Corpus Callosum.*—In 3 cases the operation resulted in a unilateral disturbance of motility.

Patients 1 and 9, both of whom were predominantly right sided, were marked preoperatively by cerebral atrophy and organic defects. Subsequent to the operation patient 1 suffered right-sided paresis after numerous seizures. Patient 9 displayed transient left paresis, and later, in conjunction with jacksonian attacks, transient right hemiplegia and aphasia developed. Patient 12 suffered retrograde thrombosis of one of the cerebral veins in the frontal lobe, and hemiparesis resulted. These motor disturbances disappeared completely in patient 9 and were greatly reduced subsequently in patients 1 and 12. Since in patients 1 and 9 the motor signs developed in relation to seizures and not in relation to the side of the craniotomy or their measured laterality, we are convinced that these disturbances had nothing to do with the sidedness or "cerebral dominance" of these patients. We have already noted the changes in laterality in patient 1, which occurred in connection with the paresis of his preferred side. The shift in sidedness in this circumstance far exceeded that found in any typical case of section of the corpus callosum. The reversal of laterality in this condition affected mainly footedness, body orientation and unimanual habits. Bimanual responses were not greatly changed, and eyedness was not modified at all.

In patients 2, 5 and 15 motor disturbances which existed preoperatively (absence of deep reflexes; hemiplegic residua) were temporarily exaggerated after section of the corpus callosum. The explanation may be, as Pike and his associates [23] have shown, that an operative lesion imposed on an already present lesion (in this case pathologic) may give rise, at least temporarily, to a greater effect than the latter lesion alone. If this is true, the corpus callosum acts as an adjunct to the motor systems of the forebrain in determining skilled movement. It is possible that this explanation also applies to the postoperative onset of temporary motor disturbances in patients 1 and 9.

2. *Nature of Changes in Sidedness After Section of the Corpus Callosum.*—It is to be emphasized at the outset that to the casual observer section of the corpus callosum has little effect on the laterality and motor organization of the patient. The changes that do occur are made evident only by extensive sampling and statistical treatment of observations in over 100 different performances. Furthermore, the measured shifts in laterality thus observed are temporary.

The pertinent facts as they appear in the data seem to be as follows. Temporary instability in laterality of function appears in some patients

23. Pike, F. H.; Elsberg, C. A.; McCulloch, W. S., and Chappell, M. N.: (*a*) The Problem of Localization in Experimentally Induced Convulsions, Arch. Neurol. & Psychiat. **23**:847 (May) 1930; (*b*) Some Observations on Experimentally Produced Convulsions: II. The Type of Convulsions Elicitable After Lesions of the Rubrospinal System, with Some Incidental Findings, Am. J. Psychiat. **10**:567, 1931.

after section of the corpus callosum. Right-sided persons may not be affected at all, even though the section is complete. As judged from the results on 3 subjects, patients having any marked degree of left sidedness (i.e., left-sided and ambidextrous persons) are affected more seriously than right-sided patients. After section of the corpus callosum, mean decrease and mean increase in laterality are about equal in right-sided persons, but mean decrease is more than double mean increase in patients with notable degrees of left sidedness. After some two or three months the laterality status of the patients is readjusted, so that the preoperative laterality is approximated. The fact should be mentioned that of 2 patients showing dissociation and antagonisms of movement after operation, 1 (patient 4) was left handed.

Different aspects of motor organization are unequally affected by the operation. Eyedness and writing habits generally are not modified at all. Performances involving bimanual eye-hand coordination, unimanual tool using and manipulation and general body orientation are changed most by the operation. When the results in all the cases for all different types of performance are averaged, decreases in laterality exceed increases. This decrease is accounted for entirely in terms of the greater tendency toward ambidexterity after operation among persons possessing preoperatively mixed dominance or left sidedness.

Results obtained on patient 18 are presented to show that eyedness may be shifted after resection of one occipital lobe while the patient retains postoperatively the marked dominance of the hands and feet that he possessed before operation.

Results obtained on patient 17 are cited to prove that strong right sidedness may be present in a person with apparent agenesis of the corpus callosum. Sidedness in this patient was not changed by craniotomy and excision of a mass of cortical tissue lying between the two frontal lobes in a defect of the falx.

3. *The Basis of Temporary Shifts in Laterality After Section of the Corpus Callosum and Recovery from the Changes.*—The fact that section of the corpus callosum produces equal increase and decrease in laterality in right-sided patients and greater decrease than increase in left-sided patients argues against the belief that the section should abolish all of the learned activities of the "subordinate hemisphere," which must thereafter be relearned. It is clear that neither in right-sided nor in left-sided patients who possessed no preoperative motor deficiencies were the learned activities of the subordinate side abolished. One case in point is that of patient 15, who was right sided as a young child but shifted in sidedness because of injury to the motor centers of the left hemisphere. At 10 years of age there remained only minor hemiplegic residua of the right side. After section of the corpus callosum this patient did not lose motor ability on the left side, although

according to prevalent ideas the learned activities of the right hemisphere would be almost completely abolished since it was originally the subordinate hemisphere.

It is possible that the best explanation of the present results lies in the postulation that "inherited" sidedness is determined by paired motor mechanisms at different levels of the central nervous system, both cortical and subcortical, but that sidedness which is established through training, as in persons with mixed and left laterality, is in part controlled by paired cortical centers, integrated through the corpus callosum. In cases of such a condition section of the commissural fibers demands a period of readjustment of the cortical nuclei before the partly modified reciprocal balances and functions of the whole system are as stabilized as they were previously. Thus the observed changes in sidedness after section of the corpus callosum are best accounted for in terms of individual variation in the significance of the cortical commissural system (and hence the cortex as a whole) in motor coordination according to the inherited laterality status of the patient.

4. *The Significance of the Present Results in Relation to the Concept of Lateral Cerebral Dominance.*—At the outset, we must distinguish the general concept of the lateral cerebral control of motor function from the hypothesis that cerebral dominance (dictatorship of one hemisphere over the other) is responsible for laterality of function. The latter belief is clearly disproved by the present results, not only on general but on any number of specific grounds. The former concept, based as it is on facts that one hemisphere of the brain plays a predominant role in language functions, complex motor coordinations and higher perceptual processes, is evaluated by the present experiments in the following respects: To the extent that the concept correctly states certain facts of neurology, the present data would seem to purge the view of any implication that the predominance of one hemisphere in mediating a given function, e.g., speech, is dependent on extensive intercortical inhibition and facilitation or on education of the subordinate hemisphere by commissural paths from the dominant side. Perhaps it is feasible to reorganize the concept of lateral cerebral dominance to concur with a generally recognized fact of modern neurophysiology, namely, that different levels of the nervous system cooperate in integrating postural reactions and transient motor response in such a way that, although different levels may predominate in control of limited aspects of an organized activity, discrete division of labor between levels is lacking in the intact organism. Consideration of this point of view leads us to believe that lateral neural dominance may involve dominance of brain stem centers as well as cortical centers. In this connection, Pike, Elsberg, McCulloch and Chappell [23b] showed

that section of the commissural system of the midbrain in cats has far greater effect on motor capacity than cutting the fibers of the corpus callosum.

5. *The Nature of Sidedness in Behavior as Indicated by the Present Results.*—Many statements have appeared in the literature concerning the question whether or not behavior laterality is a unit trait. Those asserting the unitary character of sidedness ordinarily imply in their beliefs adherence to the hypothesis of lateral cerebral dominance as a basis for the imbalance between the two halves of the body.

The present study tends to deny the view that sidedness is unitary in character, as well as the view that the central balances related to different aspects of sidedness are neurologically a unitary system. The complex character of sidedness has been brought out especially clearly in relation to eye dominance and other aspects of sidedness. The profile method of measuring sidedness devised in this study shows, in addition, that many different types of motor performance display varying degrees of sidedness and are not uniformly affected by lesions of the nervous system.

In general, the results of this study and additional considerations lead us to believe that any uniformity in sidedness in the subject is probably derived from strong original imbalances in the neural mechanisms of the postural system early in life and the integration through learning of correlated lateral habits with this primary neural sidedness.

TRACTOTOMY FOR RELIEF OF TRIGEMINAL NEURALGIA

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When Sjöqvist [1] introduced tractotomy for the relief of trigeminal pain, the first cases in which operation was performed were those of postherpetic neuralgia and of painful anesthesia following section of the trigeminal root. For some time hesitation was felt in applying the new procedure to true trigeminal neuralgia, since section of the sensory root carries little risk to life and pain as a rule is permanently abolished. A follow-up study [2] of the 313 cases of trigeminal neuralgia in which operation had been performed in this clinic up to July 1, 1938 revealed that the late results were not quite so brilliant as had been supposed and particularly that the disability and discomfort due to complete or nearly complete anesthesia in the greater part of the trigeminal area were considerably underestimated. Since tractotomy held out the promise of relief from pain with conservation of tactile sensation, it was decided to give this operation a trial in a series of cases of true trigeminal neuralgia.

METHOD

The operation as originally proposed by Sjöqvist required a fairly large bone defect, as a considerable part of one cerebellar hemisphere and the region of the foramen magnum were exposed. In the absence of pressure a bone defect of these dimensions exposes the patient to the danger of a postoperative clot, and it is therefore desirable to limit the area to be deprived of its bony covering to the absolute minimum. The technical steps of the operation as now performed are as follows: A straight incision is made from a point just below the occipital protuberance to the spinous process of the third cervical vertebra (fig. 1). The soft parts are divided exactly in the midline. The insertions of the short rotators of the head are freed from the occipital bone and their origin on the atlas is divided with the diathermy needle. After a sufficient area of bone has been exposed two burr holes are made. The subsequent nibbling away of bone is much facilitated if two burr holes, instead of the customary single one, are made. Bone is then ronguered away until a sufficient area of dura is exposed (fig. 2). The posterior rim of the foramen magnum is of course removed.

From the Neurosurgical Clinic, Karolinska Institutet.

1. Sjöqvist, O.: Studies on Pain Conduction in the Trigeminal Nerve, Helsingfors, Mercators Tryckeri, 1938.

2. Olivecrona, H.: The Syndrome of Painful Anaesthesia Following Section of the Sensory Root of the Fifth Nerve in Tic Douloureux, Acta chir. Scandinav. **82**:99, 1939.

The dura is then opened by a V-shaped incision (fig. 3). The occipital sinus may occasionally be large, but hemorrhage from this source can always be controlled by silver clips. After incising the arachnoid and evacuating the fluid in the posterior cistern, the tonsil on the side of operation is gently elevated and a suitable point for incision into the spinal trigeminal tract selected. The anatomic landmarks are not clear, and the chief difficulty lies in picking out the corrcet place for making the incision. Originally Sjöqvist recommended making the incision at a level corresponding to the border between the middle and the inferior third of the olivary eminence. Experience has convinced me that this is too far craniad

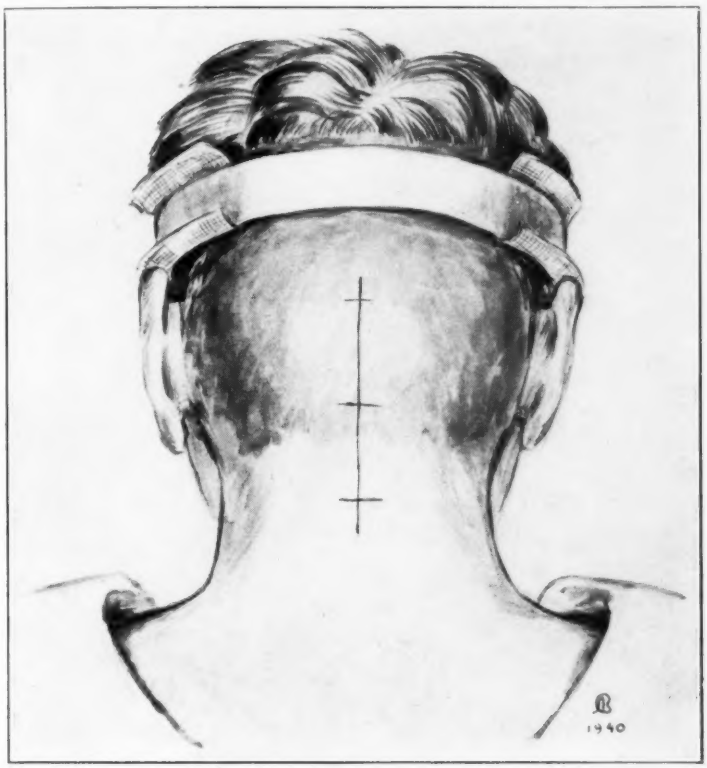

Fig. 1.—Line of incision.

(fig. 3). Besides, the olivary eminence cannot always be seen, since it may be covered by the vagus rootlets, the vertebral artery or its branches.

The lower end of the fourth ventricle is a better landmark for the frontal plane in which the incision should be made. This corresponds to the inferior pole of the olivary eminence, and the spinal trigeminal tract is therefore sectioned at a point 2 to 3 mm. caudal to that originally recommended by Sjöqvist. It should be emphasized, however, that in the cases reported the incision as a rule was made at a level considerably higher than the lower end of the fourth ventricle, since it only gradually became clear that most failures and complications were due to making the incision at a level too far cephalad. Otherwise no change has

been made in the original technic; i. e., the incision is started immediately lateral to the dorsal nucleus, and is extended ventrally to a point just dorsal to the level of the vagus rootlets. It is never necessary to make the incision more than 3 mm. deep unless the point selected is too far cephalad.

The operation is greatly facilitated by employing local anesthesia, since the pain experienced on incising the medulla is confirmation that the incision has been correctly placed. The pain is intense, but since it is of momentary duration it is usually well borne except by the most nervous and sensitive patients. It is interesting to note that the pain following cutting the spinothalamic tract is less intense;

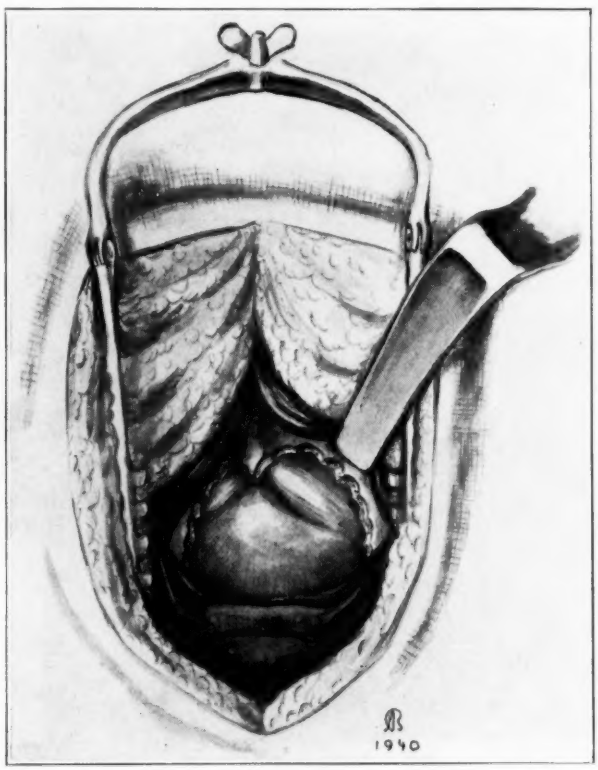

Fig. 2.—Size and form of bone defect in a case of right-sided tractotomy.

on the other hand, section of a sensory root is more painful than section of the spinal trigeminal tract.

If the incision has been correctly placed the pain felt at the moment of incision is referred to the entire trigeminal area. If pain is felt only in the first division the incision should be extended a little in the dorsal direction, since the fibers belonging to the third division lie in the dorsal part of the tract. Conversely, if pain is felt only in the third division extension of the incision in the ventral direction is indicated.

Sensation in the face is then immediately tested, and if the incision has been correctly placed the patient should be completely analgesic in the trigeminal area

on the side of operation. If analgesia is incomplete in the first or second division, although one feels sure that the incision has been carried far enough ventrally, it is inadvisable to try to obtain the desired result by deepening the incision or carrying it farther in the ventral direction. Paralysis of the vocal cord due to injury to the intramedullary part of the vagus rootlets easily results from such

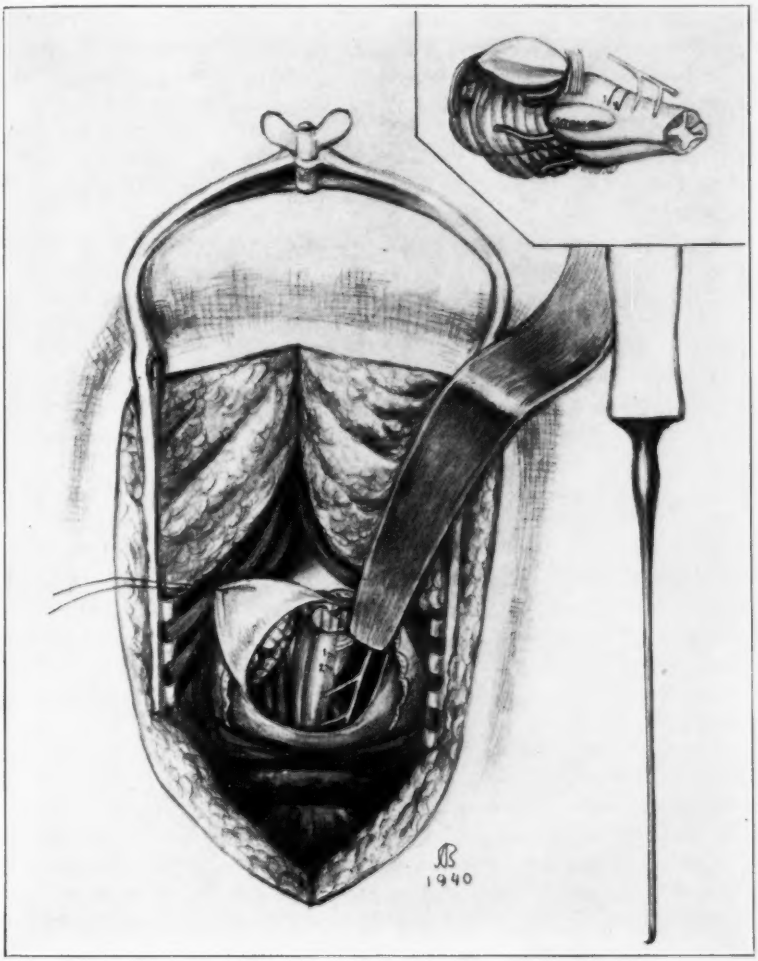

Fig. 3.—Level of incision into the medulla. *1* indicates original place of incision; *2*, level of incision now in use.

an attempt; occasionally even deglutitory difficulties occur. In some cases in which palsy of the vocal cords occurs a partial Horner syndrome is present, indicating that the incision has been too deep. If the incision has been extended too far in the ventral direction the spinothalamic tract may be injured. Judging from the experience in 1 of my cases in which this happened, the caudal segments are placed in the most dorsal part of the spinothalamic tract at this level.

If analgesia is incomplete in the first and second divisions, it is probable that the incision has been placed too far cephalad, at a level at which the spinal trigeminal tract has not yet reached the surface. The correct remedy therefore is to make a new incision 2 or 3 mm. caudal to the first one.

If, on the other hand, analgesia is incomplete in the third division one has to bear in mind that the fibers of the secondary trigeminal tract belonging to the third division begin to leave the spinal nucleus at a more cephalic level than fibers belonging to the second and first divisions. Insufficient analgesia may therefore depend on the fact that a large number of fibers have already left the nucleus to form the secondary trigeminal pathway. If a cautious extension of the incision in a dorsal direction does not yield the desired result an attempt may be made to sever the spinal trigeminal tract at a level 2 or 3 mm. cephalad to the first incision. Unless the neuralgia involves primarily the third division, this would hardly seem to be necessary.

In concluding, it should be emphasized that an incision which has resulted in an unsatisfactory degree of analgesia should be corrected not by deepening the incision beyond 3 mm. or by extending it beyond the prescribed limits in a dorsal or ventral direction but rather by making a new incision cephalad or, usually, caudad to the first one.

Hemorrhage from the incision is usually absent or very slight. Sometimes a small vein runs across the line of incision and must be divided. The resulting hemorrhage is easily arrested by placing a pledget of cotton moistened in hydrogen peroxide on the bleeding point.

When the incision in the medulla is completely dry the dura is closed with interrupted silk sutures and the muscles are stitched together in the usual fashion with interrupted silk or linen sutures (fig. 4).

During the days following operation the analgesia, even if it has been complete immediately after the incision, sometimes subsides to some extent. Occasionally only slight hypalgesia remains, indicating that the major part of the spinal trigeminal tract has escaped division. As a rule the intensity and location of the operative pain are a more reliable sign that the incision has been correctly placed than are the results of sensory tests made immediately after the incision. Obviously, the entire trigeminal tract is thrown out of action for some time, even if only part of the tract has actually been divided.

Up to Sept. 1, 1940, altogether 34 patients with true trigeminal neuralgia were subjected to tractotomy. Among these were 4 with bilateral and 30 with unilateral pain. The indications for tractotomy were comparatively broad during the last year of the period, and a number of patients were accepted for tractotomy who, in the light of the present study, probably would have been better served with section of the sensory root.

RESULTS

The data on the 30 cases of unilateral trigeminal neuralgia are summarized in the table. The 4 cases of bilateral pain are reported *in extenso* and will be commented on separately, since they represent a somewhat different surgical problem.

The reports of experiences in the literature agree that division of the spinal trigeminal tract results in dissociated anesthesia of the corresponding side of the face. The sensation of touch has generally been normal,

but Grant and his co-workers [3] found that sometimes the number of touch points per square centimeter was reduced and occasionally the threshold for touch points was increased. In the majority of my cases the sensation of touch, when tested in the ordinary manner with cotton wool, was found to be normal. In some cases, however, there was slight subjective impairment in the perception of touch, which might well have been due to reduction of the number of pressure points. With regard to the discrimination of pain, heat and cold, there was always a close correspon-

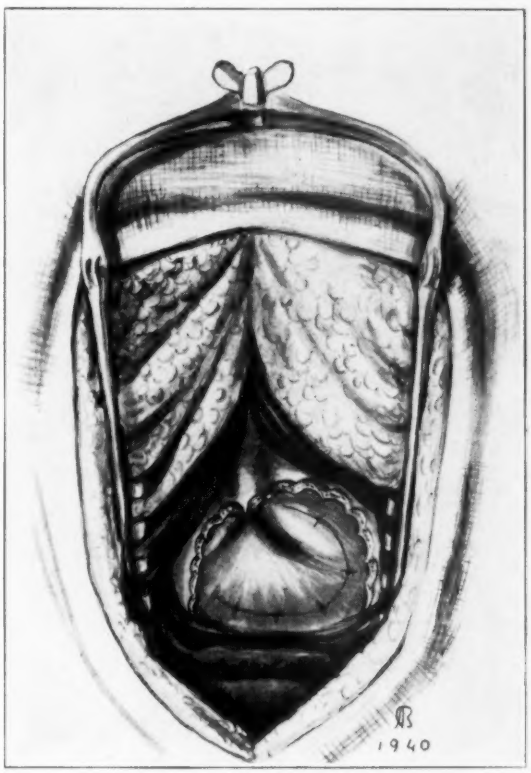

Fig. 4.—Closure of dura.

dence. If there was complete analgesia the patient was quite unable to distinguish between heat and cold and vice versa. Also, when the analgesia and thermanesthesia were incomplete there was a close correspondence with regard both to intensity and to distribution of the sensory loss.

3. Grant, F. C.; Groff, R. A., and Lewy, F. H.: Section of the Descending Spinal Root of the Fifth Cranial Nerve, Arch. Neurol. & Psychiat. **43**:398 (March) 1940.

Case No.	Sex; Age, Yr.	Duration of Illness, Yr.	Intensity of Pain	Division of Fifth Nerve Affected	Previous Operations	Level of Tractotomy Above or Below the Lower End of Fourth Ventricle	Distribution and Grade of Analgesia After Tractotomy * Divisions of Trigeminal Nerve I	II	III	Corneal Reflex	Time of Observation After Tractotomy
1	M; 69	1	Moderate	II	—	8 mm. above	+++	+++	++	..	2 yr.
2	F; 53	12	Moderate	II	—	4-5 mm. above	+++	++	+	Lost	2½ yr.
3	M; 55	9	Severe	II	—	7 mm. above	—	—	—	Normal	2 yr.
4	F; 48	3	Moderate	II	—	6 mm. above	+	—	—	Sluggish	3 yr.
5	F; 55	14	Moderate	II	—	7 mm. above	—	—	—	Normal	2 yr.
6	F; 42	7	Moderate	II	Two alcohol injections	6 mm. above	+	+	+	Normal	2 yr.
7	F; 48	10	Moderately severe	I	—	2 mm. above	+++	+++	+++	Lost	14 mo.
8	F; 55	2	Moderate	II	—	2-3 mm. above	+++	+++	+++	Normal (?)	15 mo.
9	F; 55	5	Severe	II	—	4-5 mm. above	+++	+	+	Diminished	18 mo.
10	M; 44	2	Severe	II	Extraction of teeth	3-4 mm. above	—	+	+	Present	15 mo.
11	F; 46	10	Extremely severe	III; later II also	Alcohol injection, with relief for 8 yr.	5 mm. above	+++	+++	+++	Lost	..
12	M; 54	2	Severe	II	—	Level with lower end of 4th ventricle	—	+	+	Normal	14 mo.
13	F; 52	12	Moderate	II; III	Injections of alcohol, with temporary relief	Two incisions, first 5-6 mm. above, without painful reaction; second 2 mm. above	+	+	+	Slightly diminished	13 mo.
14	F; 54	3	Severe	II; III	..	4 mm. above	++	+++	+++	Diminished	11 mo.
15	F; 67	6 mo.	Moderate	II	—	3 mm. above	+++	++	+	Lost	10 mo.
16	M; 52	2	Moderate	II	—	4 mm. above	+++	+++	+++	Greatly diminished	11 mo.
17	F; 62	13	Moderate	II	—	4 mm. above	+	+	+	Diminished	11 mo.
18	F; 64	7	Moderate	II	—	5 mm. above	++	+++	+++	Diminished	10 mo.
19	F; 59	10	Moderate	II	—	5 mm. above	+++	+++	+++	Greatly diminished	11 mo.
20	M; 44	3	Severe	II	Extraction of teeth; injection of alcohol	4-5 mm. above	+++	+++	+++	Lost	8 mo.

* The Roman figures signify the first, second and third divisions, respectively, of the trigeminal nerve.

Time of Observation After Tractotomy	Recurrence	Secondary Operation	Disturbance of Equilibrium	Paralysis of Vocal Cords	Horner Syndrome	Other Complications	General Impressions of Result
2 yr.	—	—	—	—	—	—	Excellent
2½ yr.	—	—	Slight difficulty in walking in darkness	+	—	Very slight paresthesias	Good
2 yr.	Immediate	Subtotal division of sensory nerve	—	At first present; disappeared after 2 mo.	—	—	Poor
3 yr.	After almost 3 yr. recurrence of pain for 2 mo., but not nearly as severe as before	—	Some disturbances at first, disappeared after few months	—	—	—	Satisfactory
2 yr.	Previous incision in medulla deepened; recurrence 2 yr. after second operation	After second operation slight hypesthesia in all 3 divisions	Slight to moderate during first month; disappeared later	—	—	—	Poor
2 yr.	—	—	Temporary; disappeared after short time	—	—	Slight paresthesias	Good
14 mo.	—	—	—	Slight	—	Slight paresthesias	Good
15 mo.	—	—	—	—	—	Slight paresthesias	Satisfactory
18 mo.	—	—	—	—	—	—	Excellent
15 mo.	Immediate; after second tractotomy twinges of pain appeared, but patient is well satisfied with result of operation	A second tractotomy; previous incision in medulla deepened; after second operation almost complete analgesia and thermanesthesia	Slight at first; disappeared after few weeks	—	—	Double vision during first few weeks after operation	Satisfactory
"	In spite of almost complete analgesia pain recurred in II division 3 days after operation	Section of sensory root in posterior fossa 1 week after tractotomy	—	—	—	—	Poor
14 mo.	—	—	—	—	—	—	Good
13 mo.	On two occasions severe attack of pain of same type as before operation	—	Slight at first; after 3 mo. practically normal gait and station	—	—	—	Unsatisfactory
11 mo.	—	—	—	—	—	—	Very good
10 mo.	—	—	Slight; practically normal gait and station 3 mo. later	—	Very slight	—	Excellent
11 mo.	—	—	Moderate at first; normal after a few weeks	Slight	Slight	—	Good
11 mo.	—	—	—	—	—	—	Good
10 mo.	Slight recurrence of pain 3 mo. after operation	—	Slight	—	—	—	Satisfactory
11 mo.	—	—	Moderate at first; improved after a few months	—	—	—	Good
8 mo.	During the days after operation several attacks of pain of same type as before; gradually these attacks disappeared	—	—	—	—	—	Good

Case No.	Sex; Age, Yr.	Duration of Illness, Yr.	Intensity of Pain	Division of Fifth Nerve Affected	Previous Operations	Level of Tractotomy Above or Below the Lower End of Fourth Ventricle	Distribution and Grade of Analgesia After Tractotomy * Divisions of Trigeminal Nerve I	II	III	Corneal Reflex	Time of Observation After Tractotomy
21	M; 46	3	Severe	II	—	4 mm. above	—	++	+++	Normal	8 mo.
22	F; 62	10	Moderate	II	Extraction of teeth	3-4 mm. above	—	—	—	Slightly diminished	7 mo.
23	F; 63	8	Severe	II	—	3 mm. above	+++	+++	+++	Lost	6 mo.
24	M; 67	2	Moderate	II	Several injections of alcohol	3-4 mm. above	+++	+++	+++	Lost	6 mo.
25	F; 67	3	Severe	II; III	—	5 mm. above; no painful reaction; new incision 2 mm. above	+++	+++	+++	Lost	6 mo.
26	M; 43	6	Severe	III	Several injections of alcohol	3-4 mm. above	+++	+++	+++	Lost	7 mo.
27	F; 65	12	Severe	II	Extraction of teeth	5 mm. above	+++	+++	+++	Lost	6 mo.
28	F; 65	13	Severe	II; III	Extraction of teeth	5 mm. above	+++	+++	+++	Lost	6 mo.
29	F; 64	1	Severe	II	—	4-5 mm. above	+++	+++	+++	Lost	6 mo.
30	M; 52	17	Moderate	II	—	3 mm. above	++	++	++	Lost	4 mo.

* The Roman figures signify the first, second and third divisions, respectively, of the trigeminal nerve.
† In this case a small artery lying on the dorsal surface of the medulla was torn when the arachnoid was opened. Hemorrhage was checked by packing while incision in the medulla was made. When the packing was removed hemorrhage started again and spread into the subarachnoid space on the base of the brain, causing protrusion of the exposed

In 18 of the 30 cases of unilateral pain analgesia was complete in the affected division and, with 1 or 2 exceptions, in the rest of the trigeminal area. In 1 of these (case 10) a second tractotomy was done a few days after the first, which had not materially affected sensation in the face. At the second operation the incision in the medulla was deepened, which resulted in almost complete analgesia in all three divisions.

In 3 cases (15, 21 and 30) analgesia was moderate to subtotal. In 6 cases (4, 6, 9, 12, 13 and 17) there was slight to moderate impairment of the perception of pain, and in 3 cases (3, 5 and 22) sensation finally was not affected at all. The purpose of the operation, complete analgesia at least in the trigeminal division primarily involved, was effected, roughly speaking, in two thirds of the cases, while in the remaining third the operation was a failure so far as the analgesia was concerned. No doubt the difficulty in selecting the correct place for the incision was mainly responsible for these failures, and it is significant that in several of these cases the incision was made at a comparatively high level, 5 mm. or more above the lower end of the fourth ventricle. It is only fair to point out that of the 9

Time of Observation After Tractotomy	Recurrence	Secondary Operation	Disturbance of Equilibrium	Paralysis of Vocal Cords	Horner Syndrome	Other Complications	General Impressions of Result
8 mo.	—	New tractotomy 2 mm. below first; complete analgesia in entire trigeminal region resulted	Pronounced at first; after 2 mo. normal gait and station	—	Slight	Analgesia and thermal anesthesia contralateral half of body below second lumbar segment	Satisfactory
7 mo.	—	—	Pronounced at first; after 3 mo. practically normal gait and station	—	—	—	Good
6 mo.	—	—	Some disturbances of gait and station, which gradually improved but still persisted to some degree 6 mo. after operation	+	Slight	Some disturbance of sensation in contralateral leg; slight keratitis	Satisfactory
6 mo.	—	—	Marked instability of gait and station, which gradually disappeared	—	—	—	Good
6 mo.	—	—	Pronounced giddiness with vomiting persisted for several weeks after operation; disturbance of gait and station marked; patient unable to walk without support 13 mo. after †	—	—	—	?
7 mo.	—	—	Disturbances of equilibrium marked at first; after 2 mo. normal gait and station	—	—	—	Good
6 mo.	—	—	Very slight at first; disappeared in a few weeks	—	—	—	Good
6 mo.	—	—	Moderate at first; later improved	—	—	—	Good
6 mo.	—	—	?	Slight	—	Slight paresthesias	Satisfactory
4 mo.	Occasional slight twinges of pain	—	—	—	—	—	Good

part of the cerebellum. The bone defect had to be enlarged over most of the left hemisphere and the dura widely opened before the clot could be removed and the hemorrhage finally checked. This operative complication probably accounts for disturbances of gait, station, etc., which followed operation.

failures 7 occurred among the first 15 cases in which operation was performed. With increasing experience it was gradually realized that nothing could be gained by trying to divide the trigeminal tract at the highest possible level and that attempts in this direction were too frequently attended by palsy of the vocal cord and other complications to be justified. However it was not until operation had been carried out in most of the cases reported in this article that it was found that analgesia was just as complete when the trigeminal tract was divided at the level of the lower end of the fourth ventricle as when it was divided 3 to 5 mm. higher. Obviously, comparatively few fibers leave the spinal nucleus to enter the secondary trigeminal pathway above the level of the lower end of the fourth ventricle.

Sometimes the incision may have been too superficial, as in case 10, in which the first tractotomy did no material damage to the trigeminal tract but deepening of the incision at the second operation resulted in almost complete analgesia. However, since at the level of the lower end of the fourth ventricle the trigeminal tract lies almost directly under the pia, it may also be said that the incision in this

case must have been placed too high, as otherwise an incision 3 mm. deep could not have failed to destroy the tract.

Aside from failure to accomplish analgesia of the trigeminal area, an incorrectly placed incision may have undesirable effects due to injury to important fiber tracts in the medulla. Of these, disturbances of equilibrium is the most common, as was also noted by Grant and his collaborators.[3] More or less pronounced disturbance of equilibrium was present immediately after operation in almost two thirds of the cases. The patients complained of giddiness and a sense of weakness on the side of the body corresponding to the side of operation and exhibited the typical signs of cerebellar disturbance of gait and station. In addition, dysmetria of the arm is sometimes encountered. As a rule the cerebellar disturbances are rapidly compensated and in most cases disappear completely within a few weeks. In case 25, however, giddiness, vomiting and inability to walk persisted for several months but finally improved. At this writing, six months after operation, considerable instability still persists, although the patient states that she is improving. In this case operation was complicated by hemorrhage from a small artery on the dorsal surface of the medulla, causing a hematoma around the medulla and cerebellum, which necessitated considerable enlarging of the bone defect in order to evacuate the collection of blood.

Probably the disturbance of gait and station following tractotomy is due to injury to the restiform body, another indication that the incision has been placed too high, where the trigeminal tract is still partly covered by the restiform body.

The most annoying complication, however, is paralysis of the vocal cord on the side of operation. This happened in 8 cases and must be due to injury to the intramedullary part of the vagus rootlets. In those cases in which examination of the position and mobility of the vocal cord has been made several months after operation no improvement has occurred, and the prognosis of this complication therefore appears to be poor. Since the vagus rootlets pass directly through the spinal trigeminal tract at a level corresponding to the middle of the olivary eminence, or even a little lower, it is obvious that injury to this important structure as a rule must be due to placing the incision at too high a level.

The most important point to be considered is the frequence of recurrence and the relation between recurrence and grade of analgesia.

There were altogether 8 cases of recurrence. Among these was case 10, in which the first tractotomy was a complete failure, since the pain never disappeared and the degree of analgesia was unsatisfactory. In this case the wound was reopened and the incision in the medulla

deepened, which resulted in almost complete analgesia. Since the second operation slight twinges of pain have appeared occasionally, and the case has therefore been recorded as one of mild recurrence.

Among the 8 cases of recurrence there were 4 (4, 10, 18 and 30) in which the recurring pain was comparatively slight. In these cases the patients were well satisfied with the result and a second operation did not seem indicated. In one of these (case 4) there was only a slight degree of hypalgesia in the first division, in another (case 30) a moderate degree of hypalgesia of the entire trigeminal area and in the remaining 2 subtotal or complete analgesia. In the other 4 cases (3, 5, 11 and 13) the recurrence was severe; indeed, the pain was as severe as the original one. Section of the sensory root was advised in 3 cases (3, 5 and 11) and performed in 2 of them (3 and 11). In case 5 the result was particularly disappointing, the first tractotomy being a complete failure with no analgesia and immediate return of pain. The wound was reopened and the incision into the medulla deepened, which resulted in slight hypalgesia of all three trigeminal divisions. The patient was then free from pain for two years, when she had a severe recurrence, for which section of the sensory root was advised. So far she has not been able to make up her mind to submit to further operations.

In the fourth case (13) section of the sensory root will probably become necessary.

Among the 4 cases of severe recurrence there were 2 (cases 3 and 5) in which the operation had been a complete failure, as no or very little impairment of the perception of pain had resulted, and in 1 case (13) tractotomy had led only to a slight degree of hypalgesia. Operation in these cases, therefore, must be considered as incomplete or unsuccessful. In the fourth case (11), however, in which the neuralgia was of extreme severity, the operation technically speaking was a success, as there was complete analgesia in the entire trigeminal area. Nevertheless, the pain recurred within a few days with almost the same intensity as before. The experience in this case corresponds to that in similar cases of very severe neuralgia in which partial section of the sensory root in the posterior fossa was followed by sometimes very rapid recurrence of pain when anesthesia, at least in the affected division of the trigeminal nerve, was incomplete. On the whole it seems to be true that the tendency to recurrence increases with the severity of the neuralgia and that in the worst type of neuralgia nothing but complete anesthesia in the entire trigeminal area, with the possible exception of the territory of the first division, gives adequate protection against recurrence.

It is obvious from these experiences that tractotomy carries a considerable risk of recurrence unless complete or nearly complete analgesia has been obtained. Of the 9 cases in which no analgesia or only a slight degree of hypalgesia was effected, a recurrence has already been recorded in 4, and it is quite probable that in the remaining 5 cases also pain will recur in the course of time. It is only to be expected that when the operation is technically deficient the desired result may not materialize. Rather is it a matter of surprise that in more than 50 of these cases pain did not recur at once or within a short time.

Not even complete analgesia is a guarantee against recurrence. It is significant, however, that with 1 exception (case 11) the recurrence in cases of this type has been mild and that the patients themselves as a rule have considered the operation a success in spite of the recurring pain. It is obvious from the experience in

case 11 that tractotomy should not be considered for patients having extremely severe neuralgia. Otherwise the danger of a severe recurrence appears to be comparatively slight provided a satisfactory degree of analgesia has been obtained. It must be borne in mind, however, that these patients have been observed for a comparatively short time and that any conclusion concerning the question of recurrence is so far provisional. Only after many more years have elapsed will it be possible to state definitely how great the danger of recurrence actually is.

It is obvious that the operation of tractotomy has certain drawbacks. The most serious of these disadvantages are the lesions of adjacent structures which may follow an incorrectly placed incision in the medulla. The disturbances of equilibrium as a rule disappear within a comparatively short time and are therefore of minor importance, although they undoubtedly prolong the period of convalescence and of incapacity for work. More serious is the laryngeal palsy on the side of operation, since in the majority of cases this constitutes a permanent disability. Injury to the spinothalamic tract is rare and need, therefore, not be considered as a complication of major importance.

The question of recurrence, important though it may be, is perhaps of less consequence than the lesion which an incorrectly placed incision in the medulla may produce, since in case of need recourse can always be had to section of the sensory root. Moreover, present experience, so far as it goes, indicates that the danger of recurrence is comparatively slight, provided the neuralgia is not of the most severe type and that complete or nearly complete analgesia, at least in the affected division, has been obtained. From this point of view tractotomy may be regarded as an attempt to cure the neuralgia without having to pay the price of complete anesthesia in the major part of the trigeminal area. It is true that in case of recurrence the danger to life is somewhat increased, since the patient then has to run the risk of two operations of about the same magnitude and presumably similar mortality. Certain restrictions with regard to the age and class of patients considered for tractotomy must therefore be imposed in order to reduce to a minimum the possible risk of two operations. If due consideration is given to this point the increased danger to life should be slight and well worth the great advantage that conservation of tactile sensation in the face offers.

In my opinion, therefore, the future of tractotomy mainly depends on whether accidental lesions can be avoided. The slight modifications of the original technic which have been suggested in this paper, particularly the more caudal placing of the incision and the use of local anesthesia, should eliminate entirely the danger of paralysis of the vocal cord and the disturbances of equilibrium. Injury to the spinothalamic tract is more likely to occur with a low than with a high incision, and when the incision is placed at the level of the lower end of the fourth ventricle

particular care must be exercised not to extend the incision too far in the ventral direction. This is comparatively easy to accomplish, since it is seldom, if ever, necessary to effect complete analgesia in the first trigeminal division, the fibers of which occupy the most ventral part of the spinal trigeminal tract.

It is true that to accomplish the desired result, analgesia of the trigeminal area without injury to adjacent structures, requires great precision. Although the somewhat uncertain anatomic landmarks, the small size of the trigeminal tract and the variations of anatomic structure in different cases will always make tractotomy an operation of great delicacy, it is my belief that increasing experience and familiarity with the field of operation will gradually overcome these difficulties and in the course of time make tractotomy as safe a procedure as chordotomy is today.

Since tractotomy is still in the experimental stage, it is impossible to state precise indications for its use. It is already clear, however, that patients whose neuralgia is very severe, particularly if the third division of the nerve is primarily involved, are unsuited for tractotomy. For reasons already set forth, the age and general condition of the patient should be such that section of the sensory root in case of recurrence within the next few years may be regarded as an acceptable risk. For the present, at least, it seems wise to restrict the use of tractotomy to cases of neuralgia of moderate severity in comparatively young persons, which are also those in which conservation of tactile sensation in the face is most desirable.

CASES OF BILATERAL TRIGEMINAL NEURALGIA

CASE 31.—J. M. K., a woman aged 27, for eight to ten years had had typical attacks of trigeminal neuralgia in the third division of the nerve on the right side. For five years she had had similar attacks of pain in the second division on the left side. During the last few years she had suffered periodically from painful attacks alternating between the right and the left side, occasionally occurring on the two sides simultaneously. One year ago an injection of alcohol was made elsewhere into the right gasserian ganglion, with resulting complete anesthesia of the right trigeminal area. Aside from slight paresthesias, she was free from discomfort on the right side after the injection, but on the left side the attacks continued in spite of numerous attempts to inject alcohol into the second division. She was admitted to the neurosurgical clinic on Oct. 10, 1939. There was complete anesthesia of the right trigeminal area, but neurologic examination otherwise revealed nothing abnormal.

Operation (Oct. 29, 1939).—A tractotomy was performed on the left side. An incision into the medulla was made at a level about 3 mm. above the lower end of the fourth ventricle, starting immediately lateral to the dorsal nucleus and

extending 2 mm. in the ventral direction. At the moment the medulla was incised the patient complained of pain in the entire left side of the face. The incision was deepened with blunt instruments to a depth of about 3 to 3.5 mm.

Two days after operation there was an eruption of herpes on the left side of the lower lip. The corneal reflex was lost and there were almost complete analgesia and thermanesthesia within the region of the first trigeminal division on the left and slight to moderate analgesia with almost normal differentiation of heat and cold within the distribution of the second division. In the area of the third division all forms of sensation were entirely normal. Within the hypalgesic area there was slight subjective decrease in the sensation of touch.

At the time of discharge, three weeks after operation, these sensory changes were unaltered and the patient had been free from pain.

According to letters, the pain returned about four months after operation, when she had a period of recurring attacks of pain in the distribution of the second division lasting for about two weeks and another period lasting four weeks shortly afterward. She was encouraged to return, but since the attacks gradually subsided, she decided to postpone her visit to the clinic and a probably necessary second intervention. At the time of this writing (December 1940) she is still free from pain.

In this case the operation failed to accomplish the desired result, analgesia at least within the area of the second trigeminal division, where there was only a moderate degree of hypalgesia. Although there has been some improvement in that the periods of pain have been shorter and have occurred less frequently, it is probable that a second operation will eventually be necessary. With regard to the existing total anesthesia of the right side of the face, a second attempt to divide the spinal trigeminal tract appears to be more desirable than section of the sensory root, which can of course always be made as a last resort.

CASE 2.—A. O., a woman aged 53, for eleven years had had periodical attacks of trigeminal neuralgia localized to the third division on the right side. The periods of pain were comparatively short and there were long intervals free from discomfort. Four years ago attacks of trigeminal pain began in the second division on the left side and were much more severe than those on the right. Periods of relief were short, never more than a few months. The pain on the right side was much less disturbing after the attacks started on the left side.

The patient was admitted to the neurosurgical clinic on Oct. 23, 1939. She was well built and in good general condition. The results of neurologic examination were negative.

Since the neuralgia was bilateral, it was planned to divide the spinal trigeminal tract on both sides. This was the first case in which a bilateral operation was contemplated, and it was thought prudent to do the operation in two sessions, dividing one spinal trigeminal tract at a time.

Operation 1 (Oct. 31, 1939).—With the use of local anesthesia, a curved incision was made extending from the tip of one mastoid process to the other, as in the usual bilateral exposure of the cerebellum. After dissecting away the muscles, a small bone defect was made to the left of the midline. When the dura was opened it was found that the vertebral artery made a curve in the dorsal

direction, covering the entire olivary eminence and pushing upward the rootlets of the vagus and the hypoglossal nerve. An incision was made in the medulla, starting lateral to the dorsal nucleus, but because of the position of the vertebral artery it was impossible to carry the incision as far ventrally as was desirable. Instead, a blunt dissector was used to make a subpial extension of the incision in the ventral direction. During these manipulations the typical pain was felt in the entire trigeminal area, and immediately afterward the patient was completely analgesic on the left side of the face.

The following day most of the analgesia of the left side of the face had disappeared, the corneal reflex was normal and there remained only slight hypalgesia, which was fairly evenly distributed over all three divisions of the nerve.

Operation 2 (Nov. 5, 1939).—With the use of local anesthesia the wound was reopened and the bone defect enlarged to the right of the midline. After opening the dura an incision was made in the medulla at a level corresponding to the middle of the olivary eminence. During the incision the patient complained of pain in the upper and the lower jaw and was afterward apparently analgesic in the entire right trigeminal area.

At the time of discharge, November 25, most of the analgesia had disappeared also on the right side. The corneal reflex was normal on both sides; on the left there was slight hypalgesia of the entire trigeminal area, and on the right, slight hypalgesia of the second and third divisions.

The patient reported in person on Sept. 9, 1940. A few weeks previously she had had a short period of her old pain in the second division on the left side. Otherwise she had been perfectly well and able to work. There had been no disturbance of gait and station at any time. The sensory changes were practically unchanged since the time of discharge.

In this case, too, the result was disappointing so far as, obviously, most of the spinal trigeminal tract escaped destruction and only slight hypalgesia remained as a result of the operation. As was to be expected under these circumstances, there has been recurrence of the neuralgia, though only for a short period. Whether another operation will be necessary remains to be seen; the type of operation best suited to the case must also depend on the type and location of the recurring pain.

Case 3.—A. B., a woman aged 47, for five years had suffered from typical attacks of trigeminal pain localized to the third division on the left side and later spreading also to the second division. Shortly after the painful attacks had started on the left side similar attacks occurred in the second division on the right side. The pain continued in irregular periods alternating between the left and the right side, being usually more severe on the left side.

Aside from the trigeminal pain, the patient suffered from slight weakness in the left leg, later extending also to the left arm. There was slight progress of the paresis, though not enough to incapacitate her to any considerable extent. She was admitted to the neurosurgical clinic on Aug. 6, 1939. Examination showed slight spasticity of the left side of the body, with loss of abdominal reflexes on both sides. Encephalograms were normal. A diagnosis of multiple sclerosis was made, and the patient was discharged, since she was free from pain at the time and did not want an operation.

The pain soon recurred, however, and the patient was readmitted on November 14. She now had frequent attacks of pain in the second and third divisions on both sides.

Operation (Nov. 29, 1939).—With the use of local anesthesia, a straight midline incision of the type already described was used. A bone defect of the same size as that shown in figure 2 was made but was symmetrically placed, and the dura was opened in V-shaped fashion. On the left side an incision was made in the medulla at a level corresponding to the border between the middle and the inferior third of the olivary eminence and to a depth of 3 mm. There was a typical painful reaction, localized to the entire left trigeminal area. An incision was then made on the right side in approximately the same frontal plane. While

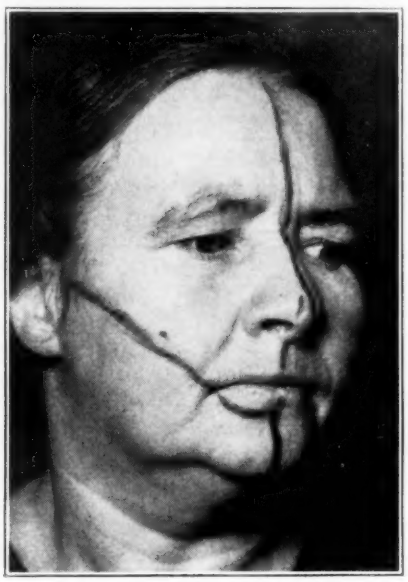

Fig. 5 (case 3).—A patient with bilateral trigeminal neuralgia. An area of hypalgesia is present on the right side.

the incision was being made the patient complained of violent pain in the second and third divisions of the nerve.

On the following day the patient was completely analgesic in the left trigeminal area, with loss of the corneal reflex. On the right side there was moderate hypalgesia and the corneal reflex was present though sluggish. During the first few days the patient had difficulty in swallowing, but this cleared up spontaneously after a few days of nasal bleeding. At the time of discharge, on December 11, there was complete analgesia over the entire left trigeminal area. On the right side there was slight to moderate hypalgesia within the area demonstrated in figure 5. The border of this hypalgesic area was indefinite, however. The corneal reflex was lost on the left and moderately diminished on the right. The patient was free from pain. There was considerable instability, and she could walk only with

support. Three months later she reported that she still felt giddy but that gait and station were improving. A year after operation she reported that she had some slight paresthesias, particularly around the left side of the mouth. The lips felt stiff. There had been no return of the old pain. Her balance still left much to be desired. She could walk alone and without support but still felt giddy.

The incision in this case was no doubt made at a level too far cephalad, with resulting injury to the restiform body, the functional effect of which has not yet, one year after operation, been fully compensated. Judging from experience in other cases, it seems probable that complete control of balance and stability will gradually be regained. With regard to the neuralgia the result may be considered satisfactory. There has been no return of pain, and the slight paresthesias the patient now experiences are not disturbing. Although there was difficulty in swallowing during the first few days after operation, the bilateral tractotomy was well tolerated.

CASE 4.—A. B., a woman aged 47, eighteen years ago began to suffer from trigeminal neuralgia on the right side, localized to the third division of the nerve. The neuralgia was severe, and she was operated on in this clinic in May 1932. About two thirds of the sensory root was divided in the posterior fossa. There resulted slight hypesthesia for all qualities, most marked in the first division, and considerable decrease of the corneal reflex. She was well for about a year, when the painful attacks on the right side returned with their old intensity. One year later attacks of the same type started on the left side, also in the third division of the nerve. Since that time she has been suffering periodically from trigeminal pain on both sides, the pain usually being more severe on the left. The periods were comparatively short, however, until about a year ago. Since that time she has been suffering almost continuously. She was readmitted to the neurosurgical clinic on Jan. 21, 1940.

On the right side there was, as related before, slight hypesthesia of the entire trigeminal area, with decrease of the corneal reflex. In addition, she had slight spastic paresis of the left leg, of obscure origin, which was present also at the time of her first admission. Otherwise neurologic examination revealed nothing abnormal.

Operation (Jan. 29, 1940).—With the use of local anesthesia, a straight midline incision was made and the region of the foramen magnum exposed. A small bilateral bone defect was made and the dura opened in a V-shaped fashion. On the right side an incision was made in the medulla at a level 2 to 3 mm. above the lower end of the fourth ventricle. There was the characteristic painful response referred to the entire trigeminal area, with complete analgesia on testing. An identical maneuver was carried out on the left side, with similar results.

The patient was discharged three weeks later. There were complete analgesia and thermanesthesia on the right side, with loss of the corneal reflex. The sensation of touch was, as before, slightly impaired. On the left there were complete analgesia and thermanesthesia within the second and third divisions. The first division was not completely analgesic, although almost so. The corneal reflex was greatly diminished but not completely lost. She was free from pain. Gait and station were moderately disturbed. She was seen again eight months later. The pain had not returned; gait and station were normal in daylight but were slightly impaired on walking in the dark.

Tractotomy in the first 2 cases of bilateral neuralgia (31 and 32) was a complete, or almost complete, failure, as only slight to moderate hypalgesia in the affected division resulted. In both cases pain recurred within a few months, but the patients appear to have had some benefit from the operation, since in both instances the returning pain was of less intensity and the painful periods shorter than before. The reasons for failure to accomplish destruction of the spinal trigeminal tract are, of course, the same as those in the cases of unilateral neuralgia and need not be further commented on. In the last 2 cases (33 and 34) tractotomy was more successful, particularly in the last, in which a very satisfactory degree of analgesia was obtained on both sides. So far in neither of these cases has recurrence taken place.

When doing a bilateral tractotomy in one stage the operator must convince himself after the procedure has been finished on one side that the voice of the patient is perfectly clear before he cuts the trigeminal tract on the other side. Obviously, it is absolutely necessary in cases of this kind that the operation be performed with local anesthesia, as otherwise bilateral palsy of the recurrent laryngeal nerve might occur. If this precaution is observed a bilateral tractotomy in one stage appears to be as well tolerated as the unilateral operation.

The great advantage which tractotomy offers in cases of bilateral neuralgia need hardly be emphasized. A bilateral root section along the temporal route, even if there is an interval of years between the two operations, should hardly ever be contemplated. The resulting bilateral anesthesia of most of the face and mucous membrane of the mouth is a very disagreeable, and even disabling, condition, which should be avoided if possible. Section of the sensory root in the posterior fossa according to Dandy's method is a much more attractive alternative. In most of my earlier cases of bilateral neuralgia operation was done in this way, in one or two stages, according to circumstances, with, on the whole, satisfactory results. However, since the degree and extension of the sensory loss after this operation can never be accurately foretold at the time of operation, tractotomy should be given a trial before section of the root is contemplated. It is admitted that the risk of recurrence is probably greater, but the advantage of retained tactile sensation in the face is so great that this risk should be carried.

SUMMARY AND CONCLUSIONS

Discomfort due to complete anesthesia in a large part of the trigeminal area is comparatively common after section of the sensory root of the fifth nerve. Even though the original pain is as a rule permanently abolished by section of the sensory roots, the results of this operation are not quite so brilliant as has been generally assumed, chiefly on

account of the paresthesias which sometimes attend a condition of complete anesthesia. Section of the spinal trigeminal tract was therefore given a trial in a series of 34 cases, among which were 4 of bilateral pain in which operation was performed between November 1937 and July 1, 1940.

Of 18 of the 30 cases of unilateral neuralgia almost complete analgesia in the trigeminal area was obtained. Of the remaining 12 cases, analgesia was slight to moderate in 9 and sensation was not affected at all in 3. It was gradually found that failure to obtain the desired degree of analgesia was due in most instances to placing the medullary incision too far cephalad. Undesirable effects of tractotomy, particularly temporary disturbances of gait and station and paralysis of the vocal cord, occur in a considerable proportion of cases in which the incision is placed at a level corresponding to the border between the middle and the inferior third of the olivary eminence or higher. The incision into the medulla should therefore be placed at a more caudal level than was originally proposed by Sjöqvist. The lower end of the fourth ventricle is a better landmark for the level at which the incision should be made than the border between the middle and the inferior third of the olivary eminence, and it is suggested that the incision should be made at a level with or slightly below the lower end of the fourth ventricle. The lowest rootlets of the vagus nerve leave the medulla above this level, and the danger of laryngeal palsy should therefore be entirely eliminated if the incision is made at this level. Disturbances of gait and station, which presumably depend on injury to the restiform body, should also be avoided, since the spinal trigeminal tract at this level is no longer covered by the restiform body. Analgesia seems to be just as complete if the spinal trigeminal tract is divided on a level with the lower end of the fourth ventricle as if the section were higher up, and apparently comparatively few fibers leave the nucleus to form the secondary trigeminal pathway above the level of the lower end of the fourth ventricle.

If complete analgesia has not been obtained the danger of recurrence is considerable, and if the operation has resulted in little or no impairment of the sensation of pain the recurrent pain is likely to be as severe as the original one. On the other hand, if a moderate to subtotal degree of analgesia has been obtained the recurring pain is likely to be slight, and the patient in such cases may be quite satisfied with the result of the operation. In cases in which the neuralgia is of extreme severity recurrence may occur even if the operation has resulted in complete analgesia of the trigeminal area. Cases of this type therefore are unsuited for tractotomy.

The future of tractotomy depends on whether accidental injuries can be avoided. The slight modifications of technic suggested in this paper

should eliminate entirely the danger of laryngeal palsy and the disturbances of gait and station. How great the risk of recurrence actually is cannot yet be stated definitely, since the period of observation must be extended over many years before this point can be settled. So far, therefore, tractotomy may be regarded as an attempt to cure the neuralgia without having to pay the price of complete anesthesia in a large part of the trigeminal area. In those cases in which the neuralgia is of extreme severity and the age and general condition of the patient are such as to make a secondary operation within the next few years a serious possibility tractotomy is contraindicated. Tractotomy therefore is best suited for comparatively young persons with neuralgia of moderate severity.

In cases of bilateral neuralgia the indication for tractotomy is more urgent than in the ordinary case of unilateral pain because of the disability attending complete anesthesia of both sides of the face. Bilateral section of the spinal trigeminal tract can be done safely in one stage provided the operator satisfies himself after the procedure on the first side is finished that no posticus palsy has occurred.

WESTERN VARIETY OF EQUINE ENCEPHALITIS IN MAN

A CLINICOPATHOLOGIC STUDY

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Equine encephalitis is not a new disease; it has been observed in the United States for over ninety years. Its etiology was not definitely established until 1931, when Meyer and his co-workers [1] first reported the discovery of a virus as the cause of encephalomyelitis among horses and mules in the San Joaquin Valley of California. A few years later TenBroeck and Merrill [2] isolated a virus in an epizootic occurring in the eastern states. This virus proved to be immunologically distinct from the western strain isolated by Meyer. It produced a much more virulent infection, with a resultant mortality of almost 90 per cent (Feemster [3]).

Meyer [4] in 1932 first suggested that human beings might become infected with the equine virus and reported 3 cases in which he suspected such an infection. Eklund and Blumstein [5] presented the first proof that such a specific human infection might actually occur. They reported 6 cases of encephalitis occurring in Minnesota. The serum in 1 of these cases neutralized the virus of the western variety of equine encephalitis. Since this report numerous instances have been reported in which the actual virus has been isolated from the human brain at autopsy. The eastern strain of the virus has been isolated by Fothergill and his co-work-

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1. Meyer, K. F.; Haring, C. M., and Howitt, B. F.: The Etiology of Epizootic Encephalomyelitis of Horses in the San Joaquin Valley, 1930, Science **74**:277, 1931.

2. TenBroeck, C., and Merrill, M. H.: Serological Differences Between Eastern and Western Equine Encephalomyelitis Virus, Proc. Soc. Exper. Biol. & Med. **31**:217, 1933.

3. Feemster, R. F.: Outbreak of Encephalitis in Man Due to the Eastern Virus of Equine Encephalomyelitis, Am. J. Pub. Health **28**:1403, 1938.

4. Meyer, K. F.: A Summary of Recent Studies of an Equine Encephalomyelitis, Ann. Int. Med. **6**:644, 1932.

5. Eklund, C. M., and Blumstein, A.: The Relation of Human Encephalitis to Encephalomyelitis in Horses, J. A. M. A. **111**:1934 (Nov. 5) 1938.

ers,[6] Webster and Wright,[7] Fothergill [8] and McAdams and Porter,[9] while the western strain has been isolated by Howitt [10] and Fothergill and his co-workers.[11] Since the isolation of the causative agent, several reports have appeared in the literature describing the clinical features of both types of equine encephalitis occurring in man. The pathologic changes occurring within the nervous system have not been so adequately studied. Because of its greater mortality rate, many more pathologic descriptions of the eastern than of the western variety have appeared. Only one fairly brief report of the lesions in the nervous system produced by the western strain of the virus in man has been published by Fothergill and his co-workers.[11]

Cases of equine encephalitis in man have been prevalent in the midwestern states for many years. Breslich, Rowe and Lehman [12] reported 101 cases occurring in North Dakota in 1938. These authors described 23 cases which came under their personal observation; in 6 cases the serum neutralized the western strain of the equine encephalomyelitis virus. During the summer of 1941 a similar but much more severe epidemic occurred in Minnesota and North Dakota. In this epidemic to date 1,700 cases have been reported, with 150 deaths. This epidemic has been identified as being caused by the western strain of the equine encephalitis virus both by the isolation of the virus from the brains of patients who died and by the detection of neutralizing bodies in the serum of the convalescing patients. The clinical features of the disease have been surprisingly uniform from case to case and, although not diagnostic, have been suggestive of the equine type of encephalitis in cases occurring in regions where exposure to the infection was possible. The pathologic changes in the fatal cases were also uniform, and certain of the histopathologic features in themselves seemed to us almost diagnostic of this illness. We have had the opportunity to study in some

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7. Webster, L. T., and Wright, E. H.: Recovery of Eastern Equine Encephalomyelitis Virus from the Brain Tissue of Human Cases of Encephalitis in Massachusetts, Science **88**:305, 1938.

8. Fothergill, L. D.: Equine Encephalomyelitis in Man, Tr. Am. Neurol. A. **65**:9, 1939.

9. McAdams, J. C., and Porter, J. E.: Encephalitis in Man Caused by the Virus of Equine Encephalomyelitis, New England J. Med. **221**:163, 1939.

10. Howitt, B.: Recovery of the Virus of Equine Encephalomyelitis from the Brain of a Child, Science **88**:455, 1938.

11. Fothergill, L. D.; Holden, M., and Wyckoff, R. W. G.: Western Equine Encephalomyelitis in a Laboratory Worker, J. A. M. A. **113**:206 (July 15) 1939.

12. Breslich, P. J.; Rowe, P. H., and Lehman, W. L.: Epidemic Encephalitis in North Dakota, J. A. M. A. **113**:1722 (Nov. 4) 1939.

detail 10 cases of western equine encephalitis in man, in 5 of which the termination was fatal. Of the fatal cases, the virus was isolated in 1 and neutralizing antibodies were found in the serum in another. However, the similarity of the pathologic lesions in all the fatal cases, as well as their resemblance to the lesions reported in the horse, leaves no doubt as to similarity of the illness in all these patients. In only 1 of the 5 nonfatal cases of encephalitis were neutralizing antibodies detected in high titer in the serum. Nevertheless, we feel that the similarity of the clinical features, as well as the occurrence of the cases among farmers from localities where equine encephalitis was prevalent, makes it highly probable that all the patients were suffering from a similar illness. In view of the paucity of detailed clinical, and especially of pathologic, descriptions of the western type of equine encephalitis in man, we feel that a review of our cases is warranted.

REPORT OF CASES

CASE 1.—*History.*—B. B., a 55 year old physician, was admitted to the hospital on July 22, 1941. Ten days prior to admission a mild headache developed. The headaches gradually became more intense, persistent and generalized and were associated with fever, chills and mild nausea. His temperature ranged between 102 and 103 F. He discontinued work and went to bed. Three days after the onset of his illness somnolence appeared and became prominent. He was then hospitalized.

Examination.—Neurologic examination revealed only general hyporeflexia. The spinal fluid was clear and contained no cells. The white blood cell count was 30,000 per cubic millimeter, with 65 per cent polymorphonuclears. The patient was transferred to the University Hospital on July 22. At this time he was very drowsy and still complained of headache. Aside from a stiff neck, the neurologic examination revealed nothing abnormal.

Course.—Somnolence persisted for six days and then gradually receded. With its disappearance the headaches also cleared up. His temperature remained normal throughout his stay in the hospital. The patient was discharged twenty-two days after admission, at which time he was free from symptoms and the white cell count had dropped to 10,200. Blood was withdrawn from the patient on July 29 and sent to the state department of health for neutralization tests; it was reported that the patient's serum neutralized the virus of western equine encephalitis.

CASE 2.—*History.*—C. K., a 59 year old farmer, was admitted to the hospital on Aug. 6, 1941. Five days before admission, after finishing his noon meal, marked dizziness suddenly developed. By the next day he was extremely drowsy and his temperature had risen to 102 F. Intense constant headache soon developed, more severe in the frontal and temporal areas but also radiating to the occipital region and down the back of the neck. There was no nausea nor vomiting. A local physician performed a spinal puncture and found 70 cells per cubic millimeter of spinal fluid.

Examination.—On admission the patient was very lethargic. The temperature was 101.8 F. There was moderately severe generalized headache. The results of

general physical examination were not significant. Neurologic examination revealed the deep reflexes to be generally depressed and the abdominal reflexes sluggish. There was generalized muscular weakness of all extremities. Sensation and coordination were intact. The neck was somewhat rigid on anteroflexion, but the Kernig and Brudzinski signs were not elicited. The spinal fluid was under normal pressure and contained 44 cells per cubic millimeter, of which 32 were mononuclears. Culture of the fluid was sterile. The white blood cell count was 8,200, with 64 per cent polymorphonuclears.

Course.—After three days of complete rest in bed the patient's temperature became normal. His drowsiness and headache also subsided slowly. He continued to gain strength and was discharged sixteen days after admission, completely recovered but still very weak.

There were many suspected cases of equine encephalomyelitis in the community where the patient lived. Several cases of mild human infection had been reported from the same area about two months previously.

CASE 3.—*History.*—R. M., an 18 year old farm boy, became ill with headaches and drowsiness one week prior to his admission. These headaches were generalized but most severe in the occipital region and were associated with some posterior cervical pain. In three days his illness had increased in severity. The temperature was elevated, and general malaise, chilly sensations and a slightly stiff neck now developed. By this time he was too ill to work, and a local physician was called, who referred him to the hospital. Two weeks prior to the patient's illness one of his horses had "blind staggers" and was treated by the local veterinarian.

Examination.—The patient was drowsy and complained of malaise, photophobia and pains in the back and limbs. Neurologic examination revealed anisocoria, the right pupil being larger than the left. There was slight weakness of the musculature of the lower part of the face on both sides. All deep reflexes were diminished. His neck was slightly stiff, with a positive Kernig sign bilaterally. Sensation and coordination were intact. The spinal fluid was normal except for 66 cells per cubic millimeter, 34 of which were polymorphonuclears. The white blood cell count was 5,300, with 72 per cent neutrophils.

Course.—Improvement was gradual. The day after his admission the patient was more comfortable, and the signs of meningeal irritation had disappeared. After six days all his symptoms had cleared up. He was discharged after a stay in the hospital of twenty-two days.

CASE 4.—*History.*—L. L., a 40 year old farmer, first had a frontal headache four days before hospitalization. The headaches increased in severity. Three days later lethargy appeared in association with general malaise, photophobia and a temperature of 103 F. On the following day some vomiting and stiffness of his neck developed. The nearest known case of encephalitis in a human being was 10 miles (16 kilometers) away. There had been some encephalitis in horses in the community, five horses being ill on the neighboring farm.

Examination.—The patient was moderately drowsy and appeared acutely ill. His temperature was 102 F., and he complained of marked photophobia. Neurologic examination revealed generalized muscular weakness. The pupils were slightly irregular. There was a questionable Babinski sign on the right. The neck was stiff. The spinal fluid was under normal pressure and contained 112 cells per cubic millimeter, with 88 per cent mononuclears. The white blood cell count on admission was 14,000, with 88 per cent polymorphonuclears.

Course.—His course in the hospital was favorable. In five days his temperature had dropped to normal, and his headache and photophobia were greatly reduced. His symptoms gradually disappeared, and he left the hospital in sixteen days, completely recovered.

CASE 5.—*History.*—E. G., a 66 year old farmer, was admitted to the hospital acutely ill on July 27, 1941. One week prior to admission mild headache, fatigue and general malaise developed. His headache increased in severity. Within a few days there appeared generalized weakness, vertigo, anorexia and vomiting. His temperature became elevated, reaching 104 F. shortly before admission. With this rapid elevation of temperature, the patient became delirious. One case of encephalitis had been reported in the patient's community.

Examination.—On admission the patient was very lethargic and when aroused appeared to be disoriented. The pupils reacted sluggishly to light. Mild horizontal nystagmus was present. There was generalized hyporeflexia, with absence of ankle jerks. There appeared to be generalized muscular weakness. Sensation and coordination appeared intact, although cooperation in tests of these functions was poor. There was no stiffness of the neck. The spinal fluid contained 23 mononuclears per cubic millimeter. The white blood cell count was 11,500, with 40 neutrophils.

Course.—The patient's condition remained unchanged for over a week, after which improvement began. His headaches and lethargy gradually disappeared, but the muscular weakness persisted and was still present at the time of his discharge, twenty-nine days after admission.

CASE 6.—*History.*—L. M. A., a 62 year old woman, was first taken ill on Aug. 16, 1941, when nausea, vomiting and severe vertigo developed while she was driving her car. On arriving home she immediately went to bed. By the next morning her temperature had risen to 101 F., and a slight headache with some lethargy had appeared. By 3 o'clock the next morning the lethargy had increased, although she could be aroused. Vomiting became projectile, respirations became labored and her temperature rose to 104 F. She was then transferred to the hospital.

Examination.—On admission the patient's temperature was 105 F. and her respirations were labored. Examination revealed extreme lethargy, but when aroused she seemed mentally clear. Her neck was very stiff, with a bilateral Kernig sign. The results of the rest of the neurologic examination were normal. The spinal fluid contained 48 cells per cubic millimeter, with predominance of polymorphonuclears. The white blood cell count was 9,000, with 74 per cent polymorphonuclears. The course was rapidly downhill, and she died on the day of admission. Brain tissue in this case was sent to the state department of health, and the virus of the western type of equine encephalitis was isolated by Dr. C. M. Eklund.

Autopsy.—Gross examination of the brain revealed its surface to be extremely congested. Cut section showed numerous distended vessels and petechiae.

Microscopic Examination.—The cerebral cortex presented few alterations. There was marked congestion of the capillaries. Many of the nerve cells showed mild chromatolysis. The cerebral white matter exhibited mild inflammatory involvement, with infiltration of perivascular lymphocytes and polymorphonuclears. Patchy areas of white substance displayed partial loss of staining properties.

The most extensive changes were seen within the region of the basal nuclei and the brain stem. Inflammatory elements were extremely numerous. Polymorphonuclear leukocytes produced many focal and diffuse infiltrations, resulting in the formation of tiny abscesses and larger areas of tissue destruction. Lymphocytes filled the perivascular spaces to form definite collars around the vessels. A few glial nodules were present. The myelin sheaths presented both patchy and diffuse demyelination. Numerous small, sharply circumscribed areas of demyelination were scattered throughout, being most numerous within the region of the basal nuclei. In some areas the myelin revealed marked loss of its tinctorial properties. In spite of the extensive destruction of myelin, there was but a minimal amount of scavenger cell reaction. Only an occasional softened area showed fat granule cells, and these were few. These myelin alterations usually occurred independently of the inflammatory changes. The vessels in this region showed definite swelling and proliferation of their lining endothelium. Some of the vessel walls were infiltrated with neutrophils. The nerve cells were not severely involved; a few displayed nuclear paling and ghost cell formation.

The changes within the cerebellum were limited to the white matter and consisted of perivascular accumulations of leukocytes and mild swelling of the oligodendrocytes.

The spinal cord showed few lesions. A few tiny foci of inflammatory elements were present within the ventral and dorsal horns and around some of the smaller vessels. There were no lesions in the white substance.

The meningeal involvement was mild, the cells being distributed in a patchy manner over the surface of the brain and the spinal cord. The inflammatory reaction consisted of a sparse infiltrate composed mostly of mononuclears. A few polymorphonuclears, polyblasts and erythrocytes could be observed throughout the pia-arachnoid.

Case 7.—*History.*—R. D., a 65 year old farmer, became ill two weeks before admission to the hospital. At that time generalized malaise and drowsiness first developed. These symptoms became progressively more severe, the patient being forced to discontinue his work and go to bed. Since his illness seemed to progress, he was brought to the hospital. On the way there he became restless and disoriented and attempted to jump out of the car.

Examination.—On admission the patient was extremely disturbed, picked at the bedclothes and talked with slurred speech. The temperature was 105 F. There was no rigidity of the neck, and Kernig's sign was not elicited. The pupils were small but reacted to light. All the deep reflexes were reduced, and Babinski's sign was not present. Sensation and coordination were intact. A spinal puncture revealed clear fluid under normal pressure. There were 107 cells per cubic millimeter in the spinal fluid, 67 of which were mononuclears. The sugar and protein contents of the spinal fluid were normal. The white blood cell count was 7,500 per cubic millimeter.

Course.—During his stay in the hospital the patient's temperature varied from 101 to 103 F. He became extremely lethargic and responded only with difficulty. Examination three days before death revealed constricted pupils, with some congestion of the fundi. The neck was now stiff, and Kernig's sign was present bilaterally. The deep reflexes were unequal, with the right biceps reflex more active than the left. There was a positive Gordon sign on the left. Drowsiness increased; respiration became labored, and the patient died five days after admission. The serum of this patient neutralized the virus of the western type of equine encephalitis.

Autopsy.—Gross examination of the brain revealed nothing significant.

Microscopic Examination.—Polymorphonuclear leukocytes were very numerous throughout the cerebral cortex, where they formed tiny abscesses and incomplete perivascular cuffs. In most areas the inflammatory reaction had not produced any parenchymal alterations. When tissue destruction did occur, microglia elements, namely microgliocytes and rod cells, were present. There was moderate astrocytic proliferation throughout the gray matter. Almost all the cortical vessels were engorged. The nerve cells displayed little or no alteration.

The cerebral white matter contained but few inflammatory lesions, only an occasional vessel showing perivascular leukocytes. However, large areas of white matter revealed diffuse tinctorial loss associated with mild glial proliferation. A few vessels showed perivascular demyelination.

The basal ganglia again revealed the most extensive alterations. The inflammatory lesions consisted of focal and diffuse collections of polymorphonuclears and perivascular accumulations of mononuclears. The walls and lumens of many vessels were filled with leukocytes. There were numerous areas of focal, diffuse and perivascular demyelination. The focal destructive lesions were extremely numerous. They consisted of small, sharply circumscribed areas entirely devoid of myelin, showing no evidence either of scavenger or of glia cell reaction. Occasionally these lesions did contain a few neutrophils or red cells. There was mild subependymal gliosis, which had resulted in the formation of an occasional ependymal granulation. Progressive changes in the ganglion cells were observed. A few large extravasations of red cells could be seen.

The brain stem did not reveal the multiplicity of lesions observed within the basal ganglia. There were scattered focal lesions composed either entirely of polymorphonuclear cells or of a mixture of pus cells, lymphocytes, microglia cells and astrocytes, the lesions composed predominantly of astrocytes forming glial nodules. Petechiae were scattered throughout this region. The tegmentum adjacent to the fourth ventricle revealed fibrillary gliosis. There were no alterations in the nerve cells.

The cerebellar involvement was limited to the white matter and consisted primarily of perivascular infiltration of lymphocytes, small abscesses and foci of demyelination. A few glial nodules containing neutrophils were observed in the vicinity of the dentate nucleus.

The entire spinal cord showed patchy involvement, the lesions being disseminated most noticeably in the central gray substance, particularly the ventral horns. The most common lesions were suppurative and consisted of small abscesses and diffuse and perivascular infiltrates of polymorphonuclear and mononuclear leukocytes. A number of small vessels showed endothelial proliferation, resulting in vascular occlusion and perivascular tissue softening. Changes in the nerve cells were minimal. The white substance of the spinal cord showed only mild swelling of its myelin sheaths.

In the meninges there was evidence of only a very mild inflammatory process.

CASE 8.—*History.*—E. S., a 46 year old farmer, first became ill on July 21, 1941. On returning from the fields early in the afternoon he complained of extreme fatigue and malaise. He immediately went to bed and slept until the following morning, at which time he continued to feel weak and dizzy. Later that morning severe headache developed and by afternoon he complained also of pains in his hands and feet. That evening he became nauseated and vomited and his temperature was found to be 102.5 F. A spinal puncture performed by the local

physician revealed 153 cells per cubic millimeter of fluid, but otherwise nothing significant. The patient was transferred to University Hospital.

Examination.—On admission the patient complained of malaise, headache, backache and severe nausea and vomiting. He was drowsy but cooperative. The temperature was 101.2 F. The cranial nerves were entirely normal. All the deep reflexes were hypoactive. The rest of the neurologic examination showed nothing significant. Spinal puncture performed three days after the onset of his illness revealed 68 cells per cubic millimeter of fluid, 59 of which were mononuclears. The white blood cell count was 7,800, with 67 per cent neutrophils.

Course.—On the day following admission the patient's temperature rose to 104.6 F. and he became very drowsy. The neurologic signs remained unchanged. Two days later, after a continued period of severe pyrexia, he became irrational and vomited repeatedly. His temperature remained persistently between 100 and 104 F., and he continued to be confused, drowsy but responsive. Lateral nystagmus was first noticed five days after admission. On the same day respiratory embarrassment with acrocyanosis developed. He was placed in a respirator and improved, but the following day his breathing again became labored and he died, one week after the onset of his illness.

Autopsy.—Gross examination of the brain revealed severe congestion of all the surface veins. Coronal sections of the right cerebral hemisphere showed a collection of petechiae in the region of the genu of the corpus callosum. Small isolated bleedings were present in all sections.

Microscopic Examination.—Throughout the entire cerebral cortex there were disseminated inflammatory lesions, composed of polymorphonuclear leukocytes arranged as small abscesses or as diffuse infiltrations between the cortical nerve cells. In an occasional purulent focus there were many proliferating glia cells, resulting in lesions resembling glial nodules. Microglia cells were also occasionally intermixed with the leukocytes in these foci. Perivascular infiltrates were not frequent and consisted only of polymorphonuclears. The small cortical vessels showed mild endothelial proliferation. The cerebral white matter showed a relative paucity of inflammatory lesions. Only one small abscess was observed, and that deep within the parietal lobe not far from the lateral ventricle. Leukocytes did, however, frequently surround the smaller vessels and in many cases actually invaded the vessel walls. A few focal areas of demyelination and a few petechiae of both the ball and the ring variety were present throughout the hemispheres.

The basal ganglia contained both focal and small diffuse infiltrations of leukocytes, as well as perivascular infiltrates of mononuclear cells. A few of the perivascular collars were comprised almost entirely of polymorphonuclear leukocytes. Large numbers of polymorphonuclears were also seen within the lamina of many of the vessels. A few macrophages, some filled with blood pigment, were visible within the perivascular spaces. Petechiae, focal areas of demyelination and diffuse areas of partial tinctorial loss were numerous, particularly near the ventricles. In the subependymal region marked cellular astrocytic proliferation had developed. Many of the nerve cells in this region displayed complete tigrolysis but were otherwise uninvolved.

The lesions within the brain stem were similar to, but much less extensive than, those described within the basal nuclei.

The cerebellum contained only a few inflammatory lesions, comprised largely of perivascular collections of neutrophils, and these lesions were entirely within its white substance.

There was mild meningeal involvement, the inflammatory elements tending to accumulate in scattered areas over the cerebral vertex and the basilar structures.

CASE 9.—*History.*—P. C., a 29 year old farmer, first had headache on July 10, 1941. These headaches gradually increased in severity and after three days became associated with vomiting, periods of unconsciousness and extreme weakness. He was admitted to the hospital on July 13.

Examination.—His temperature on admission was 102.2 F., and his pupils responded sluggishly to light. There were no other abnormal neurologic findings. The spinal fluid contained 53 white cells and 109 erythrocytes per cubic millimeter. The white blood cell count was 11,400 per cubic millimeter.

Course.—The temperature fluctuated between 100.8 and 105 F., and the patient continued to appear gravely ill. Four days after admission a convulsion suddenly developed and he died.

A horse had been sick on the farm of this patient eighteen days prior to the onset of his illness.

Autopsy.—On external examination the brain appeared extremely congested. No gross hemorrhage was observed.

Microscopic Examination.—The cortex of the cerebral hemispheres revealed only a few widely scattered abscesses. There was relatively severe vascular congestion, and many of the smaller vessels displayed marked endothelial proliferation. The walls of some of the larger vessels were infiltrated with leukocytes. Many of the cortical neurons were shrunken and showed extensive tigrolysis. The cerebral white matter was more severely involved. Small abscesses and perivascular accumulations of lymphocytes were numerous. Many scattered areas showed partial loss of their staining properties, but complete demyelination with tisssue destruction had not occurred.

The most intense lesions were present within the region of the basal nuclei and the brain stem, and these inflammatory reactions were very severe. Small abscesses and perivascular leukocytes were abundant. In addition, large areas were diffusely infiltrated with polymorphonuclears. Leukocytes were also present within the walls and lumens of the vessels and even extended into the adjacent tissues. Numerous small areas of brain tissue showed partial demyelination. Fat granule cells and often leukocytes were present within these altered tissues. Vascular congestion was marked, but actual bleedings were uncommon. There was only a minimal degree of alteration of the nerve cells. Most of the cells did not appear to be involved.

The meninges showed no signs of inflammation. There were, however, numerous erythrocytes within the subarachnoid space, the extravasations covering large areas of the brain surface.

CASE 10.—*History.*—M. E. B., a 56 year old locomotive engineer, while at work complained to his companion, the fireman, of feeling very hot. On returning home after his run he continued to complain of this symptom and of a severe headache. His temperature when taken was 104 F. The following day he was drowsy and difficult to arouse. Two days after the onset of his illness he was admitted to the hospital.

Examination.—On admission the patient was stuporous. The pupils were equal and the eyegrounds were normal. There appeared to be no involvement of the motor system. The reflexes were all normal and equal on the two sides. The neck

was very stiff, and Kernig's sign was present bilaterally. The spinal fluid was clear and under normal pressure and contained but 4 cells per cubic millimeter.

Course.—The patient died the day after admission.

Autopsy.—Grossly the brain showed no abnormalities.

Microscopic Examination.—The involvement of the cortical gray matter was not pronounced except for a few focal areas of demyelination, which were most frequent in the vicinity of the rolandic fissures. These demyelinated areas were sharply demarcated and of sufficient size to occupy more than one lamina. They were relatively acellular, containing only a few microglia cells or leukocytes. Many of the smaller cortical vessels displayed extensive endothelial proliferation with partial occlusion of the lumen. Nerve cell changes were not noteworthy, and only one small area of cortical obliteration was observed in all the sections studied. In the white matter the only prominent lesions were the perivascular infiltrates, which often completely filled the perivascular spaces and even invaded the vessel walls.

As in the preceding case, the region of the basal nuclei showed the most pronounced involvement. Here, the most extensive lesions consisted of focal and perivascular areas of demyelination. These lesions often contained microglia cells and leukocytes. There were a few scattered areas of encephalomalacia filled with fat granule cells, as well as an occasional irregular focus of parenchymal vacuolation and fragmentation. The inflammatory elements were not particularly prominent and were arranged almost entirely as perivascular or intramuscular leukocytes. In the subependymal regions there was mild glial proliferation, resulting in the formation of a few ependymal granulations. Scattered glial nodules containing a few microglia cells and leukocytes were also present throughout this region.

The brain stem contained only an occasional focus of demyelination and a few perivascular leukocytes. In the tegmental region a distinct glial proliferation and an occasional petechial hemorrhage were observed.

The cerebellar alterations were limited to the white matter, where an occasional area of tinctorial loss and a few poorly developed perivascular infiltrates could be seen.

The meningeal inflammation was mild and was present in disseminated areas over most of the brain surface. It consisted primarily of mononuclear cells intermixed with a few neutrophils.

Through Dr. H. C. Manaugh we have had the opportunity of studying the nervous system in another case of western equine encephalitis in which the virus was isolated. The lesions were identical with, although much less severe than, those already described.

CLINICAL FEATURES

The clinical picture in the 1941 epidemic of western equine encephalitis was similar from case to case. The disease usually affected adults, the ages of our patients ranging from 18 to 66 years. It has been reported in children, Davis [13] publishing a case of the disease in a 2½ month old infant. The incubation period has not been definitely estab-

13. Davis, J. H.: Equine Encephalomyelitis (Western Type) in Children, J. Pediat. **16**:591, 1940.

lished but appears to be approximately two weeks. The onset of the disease is usually sudden but not explosive, with generalized malaise and mild headache, followed occasionally by some nausea and vomiting. The temperature becomes moderately elevated, and chills may occur. After a few days the headache increases in intensity, often becoming constant and generalized and radiating to the occipital region or down the back of the neck. Drowsiness appears and may progress to fairly severe lethargy; the patient, however, usually responds to sufficiently intense stimuli. Photophobia and vertigo may form a prominent part of the syndrome, the latter occasionally being the presenting complaint. Ordinarily the symptoms persist for about ten days and then gradually subside. In the more severe form the temperature may become very high (105 to 106 F.), the headaches most intense and the sensorium cloudy, with disorientation in all fields. The lethargy commonly passes into stupor, which may alternate with extreme restlessness. In those cases in which the termination is fatal the course of the illness is usually rapid, death often occurring from four to seven days after the onset.

The only constant physical sign is mild stiffness of the neck associated with a positive Kernig sign. Generalized and severe muscular weakness may be present and often persists long after subsidence of all other symptoms. Hyporeflexia has been noted in many cases. The cranial nerves, sensation and coordination are usually not involved. Convulsions are extremely unusual but have been reported by Fothergill and his co-workers [11] and by Davis.[13] They appear much more commonly in children than in adults.

The spinal fluid is usually normal except for an increased number of cells. The cell increase is moderate, the count varying from normal to as high as 200 cells per cubic millimeter. In most cases the monocytes predominate, although occasionally when the fluid is examined early in the disease, the polymorphonuclears are numerous and comprise as high as 50 per cent of the cells. There are no changes in the pressure or in the sugar and protein content of the fluid.

The blood leukocyte count is usually normal. In a few cases of the severe type leukocytosis has been encountered, but even in these cases the differential count is normal.

Recovery, when it takes place, is fairly rapid and complete. It is yet too early to discuss the occurrence of sequels in this disease. Careful follow-up studies of the recovered patients will be necessary adequately to clarify this point. However, in children immediate residuals of damage to the brain have already been reported. Davis [13] made follow-up studies on 2 children who recovered from western equine encephalitis. The first, aged 2½ months, showed mental retardation, blindness and deafness; the second, aged 3 years, was left with permanent spastic monoplegia. No lasting sequels have, as yet, been reported in

adults. The mortality rate in this disease varies from epidemic to epidemic but has usually been about 10 per cent of the reported cases.

In most cases a fairly accurate history of exposure to the disease can be obtained. A definite etiologic diagnosis can be made by the neutralization test. Antibodies appear in the patient's blood after the first week. According to Eklund,[14] antibodies against the western strain of the virus have been found rarely in serum from persons with no history of encephalitis, so that a positive neutralization test with a clinical history of encephalitis justifies a diagnosis of encephalitis of the equine type. Isolation of the virus from the spinal fluid and from the brain tissue at autopsy has been recorded.

The clinical picture in the eastern type of equine encephalitis is remarkably different from that in the western variety. Descriptions of eastern equine encephalitis have already been published by Wesselhoeft,[15] Farber[16] and Fothergill[6] and their associates. Children are chiefly affected, the ages of Fothergill's patients ranging from 1 month to 8 years. The onset of the illness is very abrupt, with extremely high fever, vomiting, lethargy and convulsions. Within twenty-four to forty-eight hours the patient is gravely ill. The lethargy rapidly passes into a stupor. The convulsions become severe and generalized. The temperature is usually high, ranging between 102 and 104 F. Stiffness of the neck and Kernig's sign are invariably present. As the illness progresses, there may appear aphasias, diplopia and various palsies indicative of severe damage to the brain. The spinal fluid is under increased pressure, with marked pleocytosis, the count often exceeding 1,000 cells per cubic millimeter. Polymorphonuclears may predominate in the spinal fluid in the early stages of the disease. The white blood cell count varies from 13,000 to 35,600 cells (Farber and associates[16]). The course of the illness is usually fulminating, with a fatal termination in 65 per cent of the cases (Fothergill[6]). Those patients that survive often show striking residual neurologic disorders.

When one compares the clinical features of these two varieties of equine encephalitis, the differences are at once apparent and pronounced. The appearance in the younger age group, the fulminating course with a high mortality, the appearance of signs of focal damage to the brain, the diplopia, the increased spinal fluid pressure, the leukocytosis and the

14. Eklund, C. M.: Encephalitis, Minnesota Med. **24**:723, 1941.

15. Wesselhoeft, C.; Smith, E. C., and Branch, C. F.: Human Encephalitis: Eight Fatal Cases, with Four Due to the Virus of Equine Encephalomyelitis, J. A. M. A. **111**:1735 (Nov. 5) 1938.

16. Farber, S.; Hill, A.; Connerly, M. L., and Dingle, J. H.: Encephalitis in Infants and Children Caused by the Virus of the Eastern Variety of Equine Encephalitis, J. A. M. A. **114**:1725 (May 4) 1940.

appearance of severe residuals all are features that are found almost exclusively in the eastern variety of the disease.

The manner of spread of equine encephalitis has not been established. Cases of contact infection have been reported in laboratory workers by Helwig [17] and Fothergill and his associates.[11] In Helwig's case a laboratory worker was accidentally sprayed with a highly virulent chick embryo virus of the western strain and became ill fourteen days later, eventually succumbing to the disease. However, this method of infection does not seem important in the general population, and multiple cases in a single family rarely occur. The disease does not seem to be transmitted from one horse to another by contact. Kelser,[18] in 1933, demonstrated that the equine virus of either the eastern or the western strain could be transmitted in laboratory animals by several varieties of Aedes mosquitoes. These observations implicating an insect vector were confirmed by Madsen and Knowlton.[19] However, even though the mosquito can be infected under experimental conditions, no infected mosquitoes have as yet been found under natural conditions. It has even been suggested by TenBroeck and associates [20] that the horse may not be the reservoir and primary host of this virus, especially since the virus is so highly fatal to the horse and has been found in so many other animals.

Equine encephalitis occurs predominantly in the summer months and tends to disappear in cold weather.

PATHOLOGIC FEATURES

The pathologic changes in the fatal cases of equine encephalitis showed a striking resemblance from one to another and seemed to be almost diagnostic of this disease. Grossly the brain may appear normal or may show extreme vascular congestion. In an occasional case a fine film of blood covers the brain surface.

The histologic alterations in equine encephalitis vary from case to case only in their severity. The lesions do not seem to be limited to any particular region of the nervous system, although the region of the basal nuclei often is the most severely involved. There seems to be no predilection for either the white or the gray matter. The histologic alterations may be summarized as follows.

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17. Helwig, F. C.: Western Equine Encephalomyelitis Following Accidental Inoculation with Chick Embryo Virus, J. A. M. A. **115**:291 (July 27) 1940.

18. Kelser, R. A.: Mosquitoes as Vectors of the Virus of Equine Encephalomyelitis, J. Am. Vet. M. A. **82**:767, 1933.

19. Madsen, D. E., and Knowlton, G. F.: Mosquito Transmission of Equine Encephalomyelitis, J. Am. Vet. M. A. **86**:662, 1935.

20. TenBroeck, C.; Hurst, E. W., and Traub, E.: Epidemiology of Equine Encephalomyelitis in the Eastern United States, J. Exper. Med. **62**:677, 1935.

Inflammatory Elements.—The inflammatory cells consist of both neutrophils and mononuclears. Both cell types form perivascular cuffs around the small arteries and veins, the polymorphonuclear lesions being more common in the gray substance and the mononuclears showing a slight preference for the white matter (fig. 1 *A* and *B*). Frequently the mononuclears form dense perivascular collars, completely filling the perivascular spaces and resembling closely the lesions associated with epidemic encephalitis (fig. 1 *A*). The neutrophils often invade the vessel wall and even extend into the tissue about the vessels to form tiny abscesses. These cellular elements are not always perivascular but may form diffuse or focal lesions scattered throughout all areas of the brain. The focal collections of neutrophils appear as tiny abscesses and are one of the most characteristic features of this disease (fig. 2 *A* and *B*). In the more severe lesions these cellular collections are associated with tissue destruction and softening with secondary invasion of microglia elements (fig. 2 *B*). In the more chronic lesions glial elements proliferate throughout these collections of leukocytes to obliterate partially and replace them. In cases of the more severe lesions large areas of the brain tissue may be diffusely infiltrated with neutrophils, among which may be seen scattered collections of mononuclears.

Vascular Changes.—The vessels are almost always severely congested. Hemorrhages vary in their frequency from case to case. In some cases they may be entirely absent, while in others they may be so severe that they produce gross petechiae, subarachnoid bleeding and even bloody spinal fluid. There seems to be no correlation between the severity of the illness and the degree of vascular alteration and hemorrhage. The latter, when present, may vary in degree and destructiveness. The petechiae are usually perivascular and small, and the surrounding brain tissue is usually not softened and does not appear to be undergoing degeneration (fig. 3). Massive destructive hemorrhages are seldom observed, but some of the smaller ones do produce injury to the brain, with secondary reaction on the part of the brain elements. Hemorrhages are not always limited to the vessels but often form diffuse extravasations. In cases of more severe bleeding the erythrocytes occasionally completely cover the underlying tissue. Many leukocytes can be seen scattered throughout these hemorrhages. In the cortical vessels the perivascular erythrocytes often extend to the subarachnoid spaces. In the larger lesions the erythrocytes may even break through into the subarachnoid space.

The perivascular spaces are often greatly distended and present rarefied tissue for a considerable area around the vessel. These distended perivascular spaces for the most part are empty but may be filled with neutrophils, mononuclears and red cells.

Many of the smaller arterioles show swelling and proliferation of their endothelial linings, the nuclei of the endothelial cells being so swollen that they occasionally occlude the lumen (fig. 4). The larger

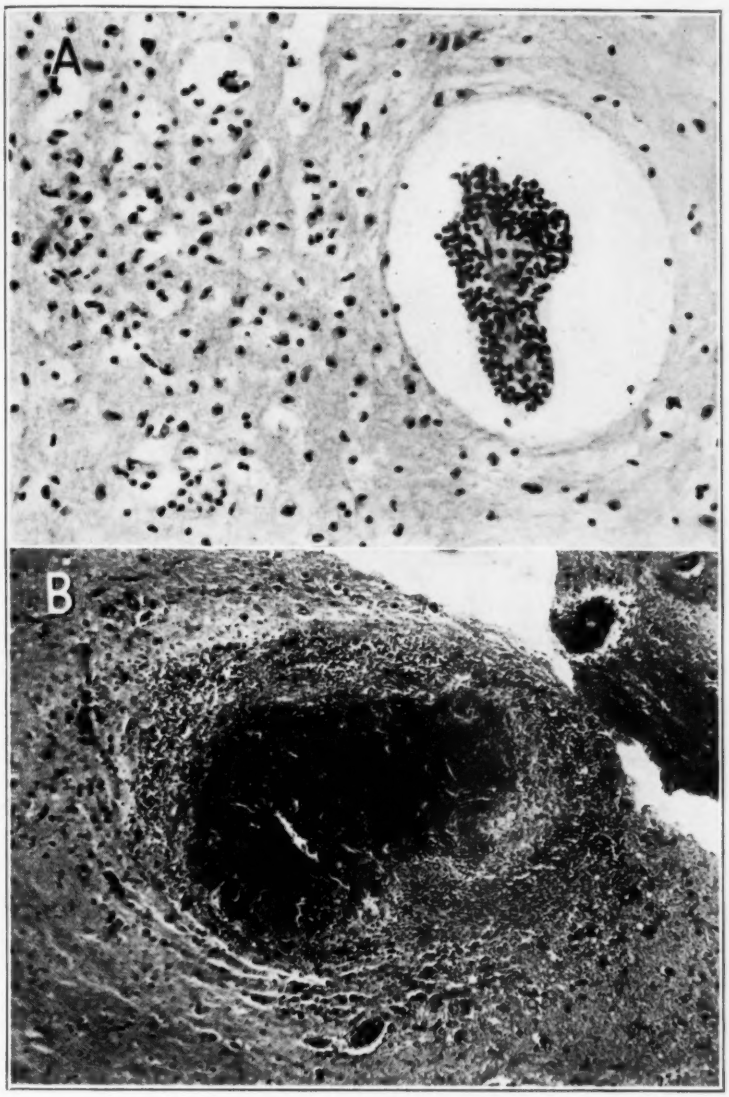

Fig. 1.—*A* (case 7), perivascular accumulation of mononuclears, resembling the cuffing of epidemic encephalitis. The tissues surrounding the vessel are diffusely infiltrated with polymorphonuclears. Hematoxylin-eosin stain.

B (case 10), thrombosis of a moderate-sized artery. The vessel walls, the perivascular space and the surrounding tissues are filled with inflammatory elements, chiefly polymorphonuclears. Hematoxylin-eosin stain.

vessels do not show this endothelial alteration, but such vessels frequently contain pus cells enmeshed within their adventitial walls. The lumens of these vessels are often filled with neutrophils, which appear as a septic

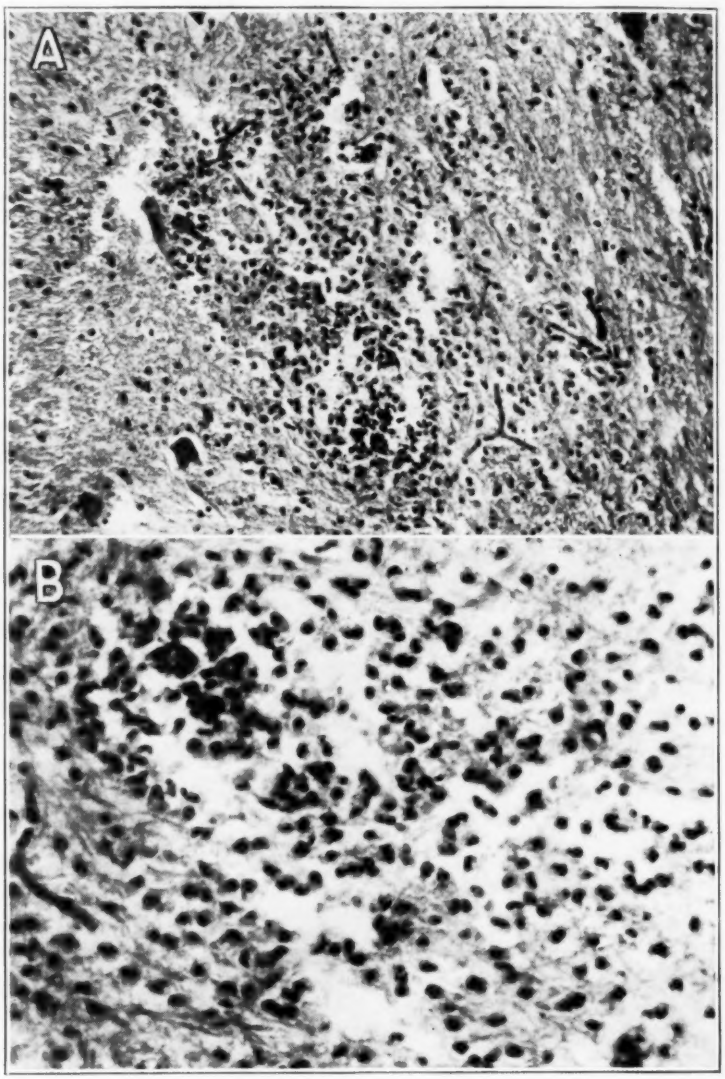

Fig. 2 (case 9).—*A*, small abscess formation. Most of the lesion is composed of polymorphonuclears, intermixed with a few mononuclear cells. Some tissue destruction has occurred. Hematoxylin-eosin stain.

B, higher magnification of the area photographed in *A*, showing cell types. Hematoxylin-eosin stain.

thrombus completely occluding the vessel (fig. 1 *B*). In some cases these neutrophils have invaded the vessel wall, producing weakening of the wall elements, with rupture and hemorrhage into the surrounding tissues. In such cases the red cells are intermixed with the white cell elements.

Myelin Changes.—Changes in the myelin usually occur early in the infection and are often extensive. They occasionally overshadow the cellular reactions and may be extensive in the presence of a minimal cellular reaction. The myelin sheaths usually present a patchy type of

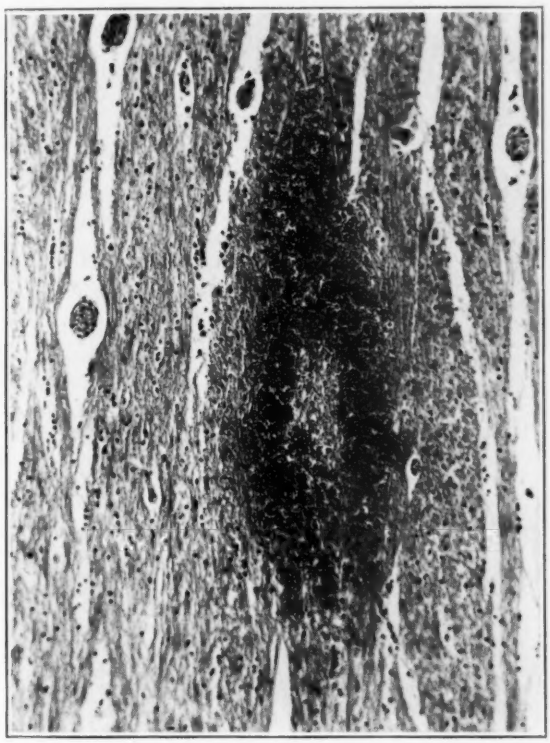

Fig. 3 (case 8).—A ring hemorrhage, with extension of erythrocytes into the surrounding tissues. There is congestion of the tiny vessels about the hemorrhage. Hematoxylin-eosin stain.

demyelination, with the production of numerous small, sharply circumscribed areas scattered irregularly throughout the entire brain (fig. 5 *A*). All stages in the destruction of the myelin can be observed, from fragmentation to complete disappearance. The earlier lesions appear merely as small softened areas filled with fat granule cells. The older lesions appear as punched-out, acellular, colorless areas. Some of these focal areas of demyelination are almost entirely filled with polymorphonuclears,

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while others contain pus cells only within their centers (fig. 5 *B*). Cavitation usually does not occur. In cases of the more fulminating type there occasionally occurs diffuse involvement of large areas of brain tissue. In these regions the myelin at first appears to lose its tinctorial properties. Later, extensive fragmentation and disintegration of the tissues occur. Usually the process seems to be so intense and rapid that fat granule cells apparently do not have time to migrate to these lesions and therefore are not seen. In none of the cases does secondary glial reaction

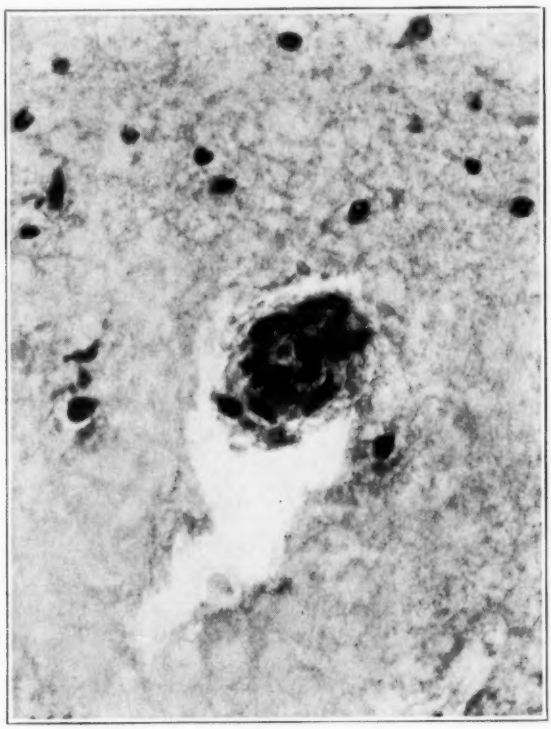

Fig. 4 (case 10).—Proliferative endarteritis. The endothelial proliferation has produced complete occlusion of the vessel, with some destruction of the adjacent tissues. Hematoxylin-eosin stain.

occur. Even the smaller, chronic areas of demyelination are entirely free of proliferative glial changes.

The blood vessels are occasionally surrounded by large areas of demyelination. Even in these lesions the pathologic process seems to be very rapid, and cellular elements are usually absent. In the earlier, less severe lesions the perivascular tissues are occasionally fragmented and filled with scavenger cells, as well as leukocytes and red cells.

Reaction of Brain Elements.—The neurons of the cortex appear generally to be unaltered structurally except adjacent to or when directly involved by a hemorrhage, plaque or inflammatory cell reaction. Some

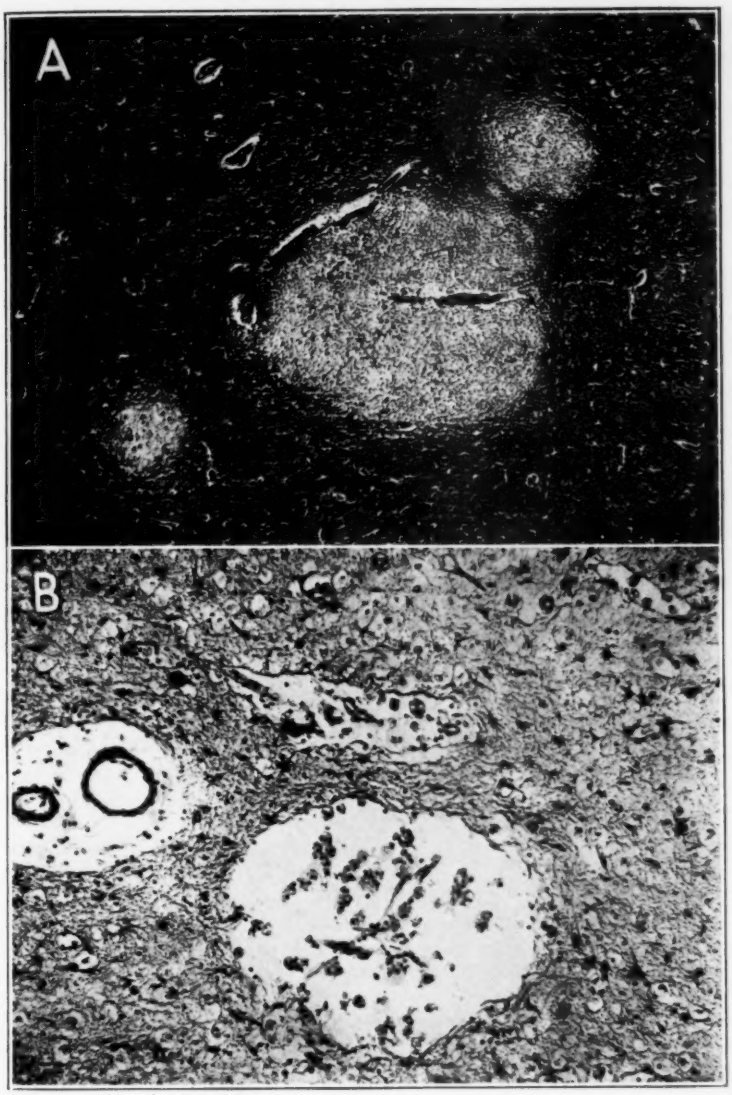

Fig. 5.—*A* (case 8), multiple areas of complete demyelination. Note the discrete, sharply circumscribed nature of these lesions, some of which are definitely perivascular. Mallory-Heidenhain technic.

B (case 10), an area of diffuse demyelination with some cyst formation. There is mild glial proliferation, with deposition of a few fibers around the larger cyst. Mallory-Heidenhain technic.

of the neurons do appear slightly swollen and chromolytic, but this change is usually diffuse. No consistent specific cytologic alterations in the ganglion cells occur. In those regions where hemorrhage or softening has involved the cortex, the ganglion cells show various degrees of alteration, consisting of fragmentation of their processes, vacuolation, disintegration and even complete dissolution and disappearance.

The macroglia also shows little specific alteration in spite of the extensive changes in the myelin. The astrocytes do not appear altered

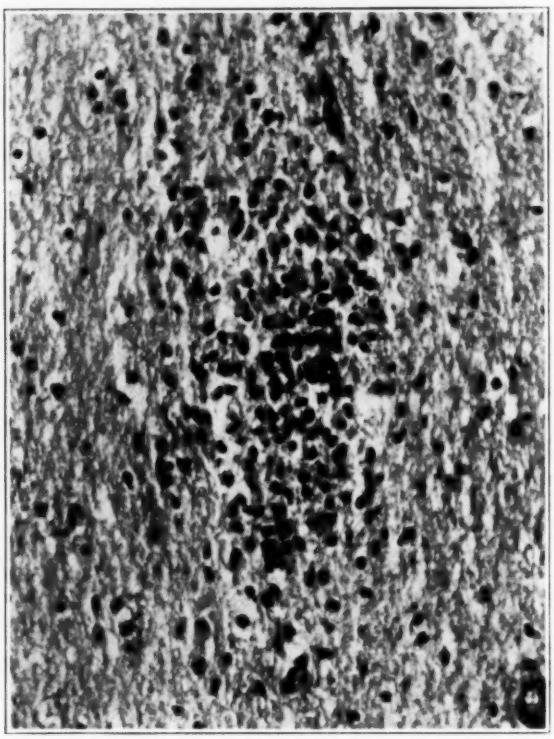

Fig. 6 (case 9).—Glial nodule. The entire lesion is composed of proliferating macroglia cells. Hematoxylin-eosin stain.

around the areas of demyelination even in cases in which the process seems to be chronic. Only in the subacute foci of polymorphonuclears do the macroglia cells undergo a rapid process of proliferation. In these areas the macroglial reaction ranges from a mild response to extensive proliferation, with replacement of the entire inflammatory focus. Glial nodules are present in all areas (fig. 6). They often contain variable numbers of microglia cells or neutrophils. Marginal glial proliferation is occasionally encountered in the subpial region.

The microglia cells reveal varying degrees of activity characteristic of phagocytosis. In view of the extensive myelin alterations, the degree of phagocytic activity is extremely mild, again suggesting that the destructive process is extremely rapid and does not allow for adequate microglial participation.

Meninges.—The most frequent meningeal involvement consists of the presence of subarachnoid bleeding. In spite of the severity of the intracerebral involvement, the meninges as a rule show but a minimal degree

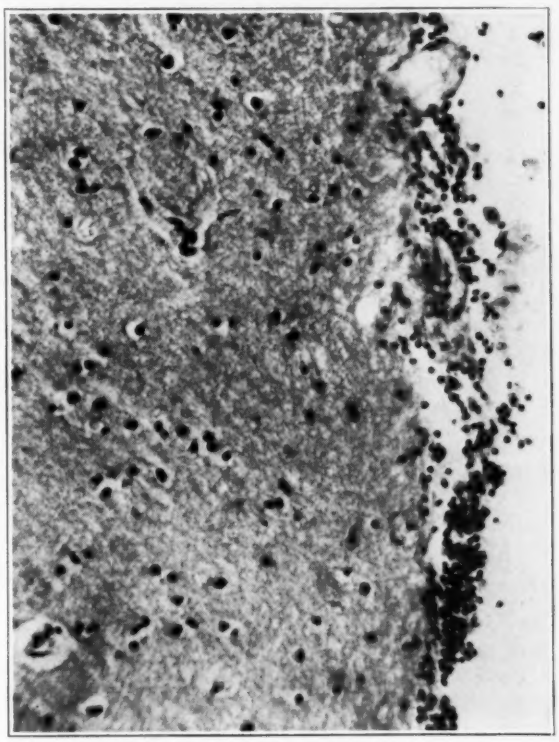

Fig. 7 (case 7).—Meningeal involvement. The inflammatory reaction is mild and composed mostly of mononuclear cells. Hematoxylin-eosin stain.

of change. There may be mild infiltration with mononuclear cells, but rarely does one encounter extensive meningitis (fig. 7).

Spinal Cord.—The cord may show disseminated involvement, which is likely to be largely restricted to the central gray matter. The lesions consist of both lymphocytes and polymorphonuclear leukocytes, which may be perivascular, focal or diffuse. Swelling and proliferation of the endothelial lining of the small vessels are not infrequent. The ganglion cells are usually not altered (fig. 8).

It might be well at this time to summarize briefly the cerebral changes that have been reported in cases of the eastern type of the encephalitis, so that one may compare the two diseases in human beings. Histopathologic changes in the eastern variety have been recorded by Wesselhoeft [15] and Farber [16] and their associates. Grossly the brain appears markedly congested and on section is softer than normal. In contrast to the western variety, there occurs widespread involvement of the nerve cells, varying from early nuclear changes to complete dis-

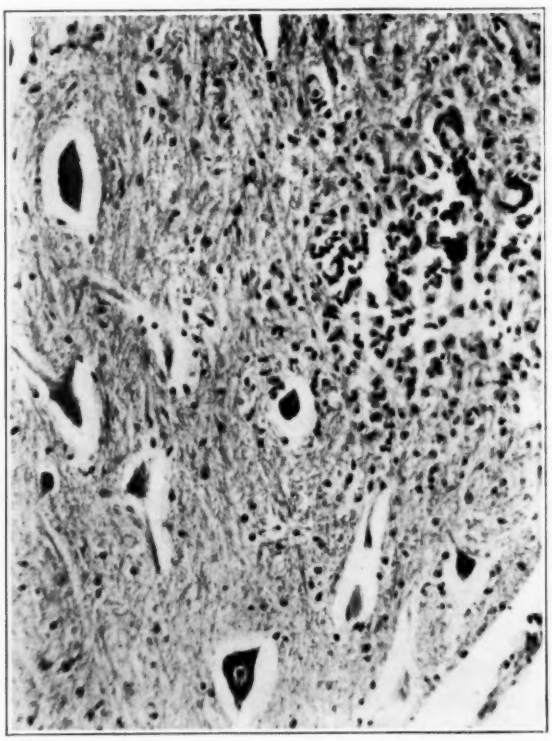

Fig. 8 (case 10).—Anterior horn of the cervical portion of the cord, showing a small focus of inflammation. Note that the nerve cells are remarkably intact. Only a few in contact with the inflammatory elements show definite alteration. Hematoxylin-eosin stain.

appearance of cells. Many polymorphonuclears are observed among the dying cells. The presence of leukocytes also comprises a prominent part of the pathologic picture in the eastern variety of the disease. These cells fill the perivascular spaces and often infiltrate the walls of the vessels to produce acute arteritis. In the severe forms of the disease these pus cells infiltrate diffusely all areas of the brain. Demyelination alone is not prominent except where destruction has occurred as a result of the

inflammatory process. In the eastern type the subarachnoid space invariably shows diffuse meningitis, which is most marked over the base. Within the meshes of the meninges are large numbers of lymphocytes, monocytes and neutrophils, with the lymphocytes predominating. The distribution of the lesions is generalized, the maximum involvement occurring in the basal ganglia, pons and medulla. Lesions have been reported in the nuclei of the cranial nerves, the cerebellum and the cervical portion of the cord.

A comparison of the lesions in these two varieties of equine encephalitis readily reveals certain differentiating points. The absence of severe meningitis, the extensive myelin alterations, the paucity of changes in the nerve cells and the frequency of hemorrhages all seem to be characteristic only of the western type of the disease.

SUMMARY AND CONCLUSIONS

Ten cases of western equine encephalitis occurring in man are reported. In 5 cases the termination was fatal and complete autopsy studies were obtained.

The clinical features of this disease are surprisingly consistent from case to case. The onset of the illness is sudden, with generalized headaches, nausea, elevation of temperature and lethargy. After a week or two the symptoms subside. In about 10 per cent of cases the disease terminates fatally.

Neurologic signs consist of stiffness of the neck, muscular weakness and hyporeflexia. The spinal fluid shows moderate pleocytosis, with mononuclear cells predominant.

In the fatal cases, lesions are found scattered throughout the nervous system, being most noticeable in the region of the basal nuclei.

The histopathologic changes are characterized by the suppurative nature of the inflammatory elements. Polymorphonuclears are common and form focal, diffuse and perivascular infiltrations. Mononuclear cells may also be prominent.

Petechiae and scattered areas of demyelination are also present and in some cases overshadow the inflammatory lesions.

THE AMNESTIC SYNDROME

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In the study of memory impairment, a topic which assembles from a multiplicity of components and embraces a large portion of human activity, definitive description remains necessary before the groundwork can be established. Attempts to gain better understanding of the role of memory in the integrated behavior of the human being through the study of the amnestic syndrome have been hindered by the lack of agreement as to just what is wrong with patients with this disturbance. An effort will be made to define more clearly what essentials to ordinary mentation are absent and how the patient acts without them.

The Korsakoff, or amnestic, syndrome follows on structural damage to the brain and consists of severe impairment of memory for recent events with relative preservation of memory for the remote past. More precise observation reveals that the utilization of material which is before the patient and can be handled independent of specific recollections is fairly intact, that transient events subsequent to the trauma are recalled most poorly and that amnestic defects of varying intensity extend retrogressively but leave the remote past relatively intact. Confabulation, a requisite for the classic syndrome, is often the sign post which directs attention to the memory impairment but is not always present in mild conditions when insight is present. There are a variety of other manifestations: loss of initiative, apathy, paucity of elaboration and other indications of passivity. It has been stated,[1] "They let the world come to them and do not go to meet it." The peripheral neuritis which is often present is not the concern of this paper.

The literature concerned with the psychology of the syndrome contains numerous discrepancies of observation as well as of opinion as to how and why the memory is disturbed. What one observer regards as fundamental, another considers secondary. There is little satisfaction that the important manifestations previously listed have been properly explained or correlated. The early writers stressed the retention failure, but although retention has rarely been considered intact, its impairment has not been found sufficient to explain the syndrome and does

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1. Bürger-Prinz, H., and Kaila, M.: Ueber die Struktur des amnestischen Symptomenkomplexes, Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:553, 1930.

not add to the understanding of the retrogressive difficulties. Bürger-Prinz and Kaila,[1] in the most exhaustive attempt to understand the interrelationships of the symptoms, reached the conclusion that the core of the disturbance lay in the passivity and diminution of drive and affect, with resultant inability to shift the orientative set spontaneously. Van der Horst [2] called attention to the sweeping effects caused by the failure to appreciate the temporal sequence of events, a fact previously noted by Gregor,[3] among others, and expressed the belief that the loss of a "time sense," evidently in the nature of a kantian category, gave rise to the remaining disturbances. Pick [4] emphasized the inability to connect thoughts properly and the contradictions which arose from the failure to dismiss an idea once it appeared. Grünthal,[5] following the trend started by Pick, found that the difficulties arose from "the lack of associational connections between the concept or thought which has just arisen and the total experience—to a certain extent thinking goes on in a single line and the necessary collateral connections do not flow into the stream of thought from all sides. . . ." The formulation in gestalt terms by Bürger-Prinz and Kaila that the patient is too possessed by a single figure, with the background too hazy, to permit ready alteration of content [1] seems essentially similar to Grünthal's concept. Hartmann and Schilder [6] expressed the opinion that repression of undesired material is a factor in the retrogressive amnesia and confabulation. Bender, Curran and Schilder stated the belief that the syndrome is to be explained not on the basis of the fading of memory traces alone but by a new type of organization of the traces.[7] Nowhere in the literature on the amnestic syndrome is there found the broad concept of the role of memory in human activity as one of the means of release from present time and place and as an integral part of the entire life of the person, as expressed in Bartlett's study of remembering in normal persons.[8]

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2. van der Horst, L.: Ueber die Psychologie des Korsakowsyndromes, Monatschr. f. Psychiat. u. Neurol. **83**:64, 1932.

3. Gregor, A.: Beiträge zur Kenntnis der Gedächtnisstörung bei der Korsakoffschen Psychose, Monatschr. f. Psychiat. u. Neurol. **21**:19 and 148, 1907.

4. Pick, A.: Beitrag zur Pathologie des Denkverlaufes beim Korsakow, Ztschr. f. d. ges. Neurol. u. Psychiat. **28**:344, 1915.

5. Grünthal, E.: Zur Kenntnis der Psychopathologie des Korsakowschen Symptomenkomplexes, Monatschr. f. Psychiat. u. Neurol. **53**:89, 1923.

6. Hartmann, H., and Schilder, P.: Zur Psychologie Schädelverletzter, Arch. f. Psychiat. **75**:287, 1925.

7. Bender, L.; Curran, F. J., and Schilder, P.: Organization of Memory Traces in the Korsakoff Syndrome, Arch. Neurol. & Psychiat. **39**:482 (March) 1938.

8. Bartlett, F. C.: Remembering, London, Cambridge University Press, 1932.

It is to be anticipated that a topic as diffuse as remembering would afford ample reasons for divergent opinion, especially in view of the absence of psychologic and anatomic fundaments to form common points of departure. Discussion of the precise reasons for disagreements would be inordinately lengthy; almost all contributions have been pertinent and have furthered the understanding of the syndrome by focusing attention on important components. Certain sources of confusion remain within the scope of clinical method and observation, and it is toward the clarification of clinical study that attention will be directed primarily.

Discrepancies of observation are in part due to the divergent types of material grouped under a single heading, for almost all conditions with amnestic difficulties and confabulation have been included. Pick's [4] patient suffered from tuberculous meningitis. Grünthal's [5] formulations were drawn from the study of a post-traumatic condition in which almost certainly there were major disturbances other than the amnestic. Van der Horst [2] included patients suffering from uremia, neurosyphilis and Alzheimer's disease in the 5 cases studied. Bürger-Prinz and Kaila [1] reported on 4 patients, 2 with aphasia and 2 with a condition resultant from asphyxia. As remembering is a complex matter, it can be disturbed in a variety of ways. Although common features are present, it is clear from my observations that the block to utilization of the past does not always rest on a common basis. To minimize the errors arising from this source, the cases selected for study form a limited group within the usual definition of the amnestic syndrome in that the deficiency in utilization of time-allocated material is the most severe and striking feature. Lest more than its due be ascribed to memory, the extraneous deficits which appear uninvited are not left unrecognized.

The grouping together of cases of all degrees of severity of impairment and the transposition of conclusions drawn from study of the most severe conditions to all amnestic difficulties are frequent practices. The precise impairment of the patient and also his assets need to be correlated with the behavioral picture before sweeping conclusions can be drawn. It will be seen that the manifestations of the syndrome vary with the intensity of the deficits, and the role of the capacities which remain cannot be neglected, as many phenomena result from the attempts to fill the gaps by the utilization of what is left.

It is believed that orderly presentation of observations, with elimination of cases in which the amnestic disturbance rests on a more sweeping disorder and with regard for variations within the syndrome, will establish a clearer basis for discussion, even if lack of psychologic knowledge precludes definite conclusions. The 3 cases selected for study represent three grades of amnestic difficulty. Opportunity is thereby offered for the comparison of the nature and intensity of the disturbances

and the modes of adaptation. After the loss is described and delimited and the interrelations of the symptoms are examined in each case, the common features will be discussed.

The first patient, O. S., presented memory difficulties which were believed to be as mild as could be ascertained with certainty. He showed neither clearcut retrogressive impairment nor confabulation, and attention is centered on the alterations in personality. G. E., the second patient, with a more apparent memory impairment, suffered from retrogressive deficits and confabulated. The third patient, C. S., unable to recollect what occurred about him, was totally disoriented and confabulated at all times; his intellectual impairment clearly extended beyond the amnestic disturbance, which, however, still remained the dominant feature. Each case, in turn, allows comparison with the preceding, and there can be noted what had been added or taken away which might help explain the manifestations not present in the less severe condition.

REPORT OF CASES

In the discussion of the first case an effort will be made to outline the thinking disturbance and to indicate the involvement of the entire personality which occurs with the amnestic difficulty. Most cases are unsuited for the examination of factors which may be dependent on remembering, as there is general cerebral involvement accompanied by generalized intellectual deterioration. Here the amnestic disorder appeared in a form which was as pure as one could reasonably expect to find. Ultimate recovery afforded the additional advantage of permitting comparison of behavior during the period of involvement with the normal.

CASE 1.—O. S., aged 30, was admitted to the Springfield State Hospital on Feb. 16, 1939, seventeen days after a suicidal attempt by inhalation of carbon monoxide. He was a taxicab driver who had been unemployed for a year because of occasional epileptic attacks. A small confectionery store which supported the family was about to be foreclosed, and the patient, mildly despondent at his inability to earn a livelihood, had said that he would commit suicide to secure the insurance money for his wife. It took several hours to revive him, and on the following day it was noted that he was forgetful, confused as to time and place, apathetic and expressionless.

The period which is of interest began about a month after hospitalization, when the patient entered a phase of partial recovery in which he remained static for many months. It became difficult to note anything wrong with his memory by casual questioning. He was able to keep track of the days, appreciate the time of day, remember the visits of his wife and the news of the family which she brought and recall the most outstanding events which were used in questioning him. Digits, three items and Binet designs were well handled, and he could carry out a series of four acts on demand.

Behavior was still far from normal. There was no display of initiative, and he would sit for long periods, idly staring into space. When asked to work in

the ward he complied willingly, but on completion of the given task he again sat and stared. He rarely spoke with others but played cards when invited. His face was expressionless, and except when a question about the family difficulties moved him to tears, nothing seemed to matter.

Careful examination showed that occurrences since the asphyxiation were remembered only fragmentarily. Events which had meaning in terms of his past life seemed best remembered. Many impinging experiences disappeared without even leaving the knowledge that they had been forgotten. Time sense, a personal time sense, was shattered, for events were not remembered in the sequence in which they had happened and the recall of one event did not revive the recollection of other events sequentially connected with it. The meaning of time was retained, and he was oriented to the passage of time by reference to dates rather than by the feeling of the passage of time, perhaps because the gap between recalled incidents was not filled with minor happenings. There was no retrogressive amnesia except for a few hours preceding the suicidal attempt. Material from his earlier life was recalled in response to questions, but there was no elaboration: Visual memories of his home and various parts of Baltimore could be evoked, but little was offered without questioning. Memory for learned historical information was poor, and as it improved substantially with recovery, the deficit could not be ascribed to faulty schooling.

Discussion of test situations which were utilized in defining the range of capacities will be limited to those which seemed most pertinent and decisive. The difficulty in handling material which depended on recall as compared with the ease of dealing with that which was placed at his disposal at one time was demonstrated by contrasting two groups of procedures. General intellectual resources measured by the Binet test showed a mental age of 11 years and 4 months, and with elimination of items clearly dependent on memory the mental age rose to between 12 and 13 years. After marked improvement the score did not alter, and from observation of the patient it is believed to be a good measure of his capacities. On performance tests his work was excellent; he worked arduously without urging, seeking after high scores. The results of the Kohs block test[9] matched those of the Binet test, a result which would not be anticipated if ability to analyze and synthesize were impaired by general cortical involvement, and the score remained the same after the patient was practically recovered. On the Healy completion test,[10] which requires ability to weigh alternatives, he made an almost perfect score. On the Porteus maze test[11] he solved the most difficult maze, showing his capacity to plan toward a goal when no temporal factor was involved. It is shown that he was capable of a fairly high order of reflective thinking, in fact, better than would be anticipated from the results of the Binet test, when the material was placed concretely before him.

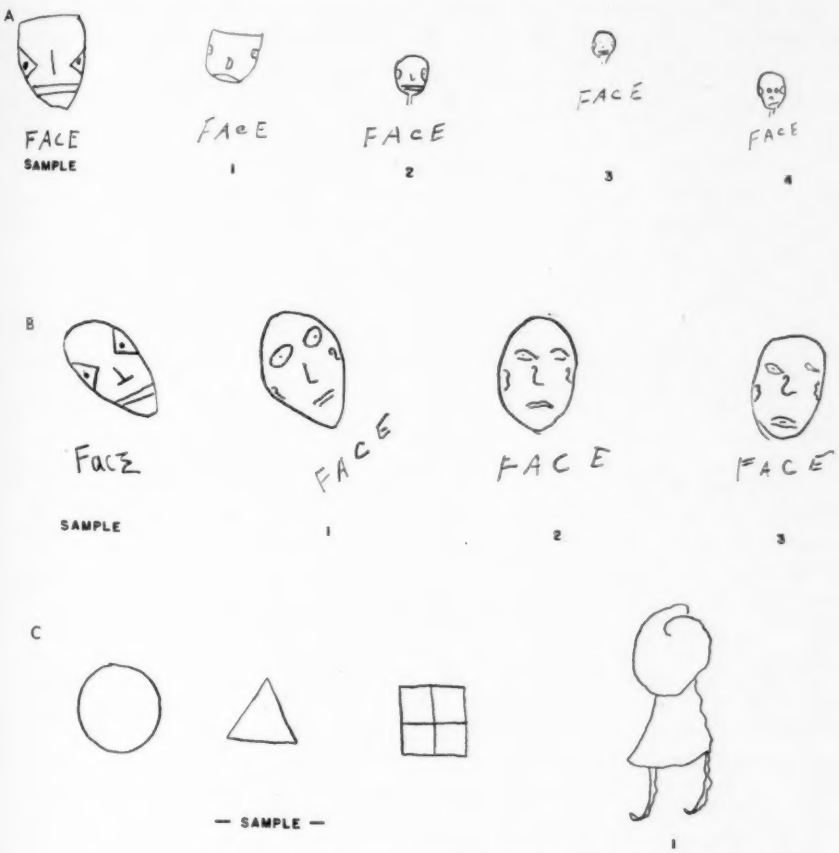
When material was offered in sequence the difference in performance was striking. When he was shown a picture, the description from memory immediately after it was withdrawn was excellent, and the registration of a visual impression was demonstrated by his ability to indicate on a blank sheet of paper

9. Kohs, S. C.: Intelligence Measurement, New York, The Macmillan Company, 1923.

10. Pintner, R., and Anderson, M. M.: The Picture Completion Test, Baltimore, Warwick & York, 1917.

11. Porteus, S. D.: Guide to Porteus Maze Test, Vineland, N. J., Training School Extension Department, 1924.

where details of the picture had been located. After three pictures had been seen and described from memory in succession, he was unable to recall the first two. It was as if the last impression had blotted out the preceding ones.[1] However, they were not blotted out, for with hints they were recalled. The longer the lapse of time after the picture was seen, the more definite were the hints necessary to effect recall. The difficulty was not limited to visual perception, for testing in similar fashion with three Binet fables produced similar results.



Memory drawings (*A*) in case 1, (*B*) in case 2 and (*C*) in case 3.

After the lapse of a day he did not remember having heard any stories, but with suitable hints they could be recalled, though not free of distortions such as are seen with normal persons after longer periods.[8] The recall of one picture or story did not lead to the next, even though the material was shown or told in the same sequence on a number of occasions.

The difficulty became more apparent when constructive recall was required. He was requested to draw an abstract figure labeled "face" from memory. After several repetitions in rapid succession, he was drawing an object closely related to a face but with little resemblance to the original drawing (figure *A*).

The implications of the deficit became apparent when a test was presented which required synthetic utilization of material presented sequentially. A comic strip was cut into individual pictures, which were then shown to the patient in sequence. Care was taken that the content of each picture was understood. To understand fully the second picture there must be a carry-over from the first, and so on, giving a cumulative effect through five pictures. After two trials he had but a vague concept of the details and no notion of the story told by the cartoon, and if pressed he was forced into weak confabulation. Details are difficult to remember unless bound together by meaning which gives coherence; as would be expected, rapid distortion of the details which were originally remembered took place. In a comic strip of "Don Winslow of the Navy," the hero and a friend are concerned about a woman who may be a spy and who has moved into the next apartment with her dog. The patient, evidently familiar with the characters, recognized Winslow but could only recall that Winslow, a lady and a dog are involved. A second cartoon, also cut into individual pictures, was given him to be pieced together into the proper sequence, a task he completed fairly well. The second comic strip was about "Scorchy Smith" on a sinking yacht. After a short interval devoted to other tests, the patient recalled having seen a comic strip of Winslow on a sinking yacht and another of a dog. Winslow had been placed on the yacht because he was a naval man. After an interval of several days the patient was shown the following instalment of "Scorchy Smith," who was still aboard the sinking yacht. He could make nothing of it, for although he could recall having seen a cartoon of a sinking yacht, it had been about Don Winslow and the two could not be related. Attempts to correct the misunderstanding only added to the confusion.

After two years the patient remains in the state hospital because occasional epileptic seizures have prevented suitable disposition. Memory function seemed intact when he was reexamined in May 1941 with comic strips and serially presented pictures and stories, although some slight impairment may remain according to the subjective account. His general demeanor has also altered in striking fashion. He is now active, jovial and talkative and is resentful that his wife refuses to take him home. He has a full grasp of the situation. He works about the hospital, running errands and laboring on the farm. The change in conversational ability seems important, for it indicates that the utilization of material from his past life had been more severely impaired than was believed at the time. In 1939 he could tell facts of his past correctly when questioned; recall was good, but there was no spontaneous elaboration. Now conversation has fulness, which gives it real meaning. When he tells that he is "down on his sisters," he goes on to explain the interfamily relationships and how he had formerly helped his sisters until the reason for his animosity is apparent. It suggests that previously he had been unable to bring into play the full associative material essential for true remembering in so far as remembering is the constructive utilization of recalled material.

The tests with the comic strips seem illustrative of the difficulties which confronted the patient in daily life because material from the past was not available spontaneously. He was unable to follow newspapers, for interpretation of news is dependent on remembering news from the preceding day; he could not follow a motion picture, which requires recollection of episode after episode. He confused the two

physicians whom he saw daily, even though he could differentiate them by name when both were before him. Despite the capacity to hold on to certain events and the general features of his surroundings, the failure to appreciate what led up to the moment left him in a vague and perplexing world.

With neglect of certain features of the case, which can better be discussed together with those of the other cases studied, attention is again turned to the accompanying manifestations of personality alteration: the loss of initiative, apathy, poverty of response and other evidences of passivity. The relative purity of the deficit in this case was shown by the excellent handling of material which was independent of recall. If there was no need to summon specific recollections, his capacity for reflective thinking was undiminished. As soon as it is realized that spontaneous mental activity is almost totally dependent on material from the past, material for comparison, elaboration, rumination, planning, etc., it is understood that the capacity to reflect which remains is of little use to the patient. The machine can run, but the feed line is broken; the loom is intact, but there are no strands to weave.

If the impression before the last can be regained only with outside aid, as shown in the test with serial pictures, the environment can have little meaning for him. The static background remains, but the events occurring in it vanish. The environment affords little stimulation, and the paucity of spontaneous recall has abolished inner stimuli. If others place a demand on him, or physiologic needs make themselves known, he is moved into activity, but otherwise he sits. There is no continuity of events because the last event is gone as he focuses on the momentary impression, and the preceding event is not available to meet the new. Continuity of time disappears with this isolation of impressions, and comprehension of meanings and of causality goes with it.

For any impression to attain fulness of meaning it must be woven into the experiences of one's life, as well as be hitched to what precedes and follows. It has been shown in this case that the recent past is not available to be connected with the new impression and that although the remote past can be recalled, it is not readily available. Whatever new integrations are formed are based on the patient's life prior to the asphyxiation, and these are sparse. He can have no full realization of the immediate situation and little stimulus to change of emotion. Little other than apathy can be expected. He does not talk to others, for there is nothing for him to talk about. There is no spontaneity, for spontaneity depends on the welling up of material from within. He is bound to others for stimulation.

If consciousness is considered as the integration of the new into the total life pattern according to dominant interests or existing schemas or engrams, such persons as the patient are in a manner only partially

conscious. The new impression is never fully perceived and therefore cannot be readily recalled. The past cannot be fully utilized, and therefore the future must remain even hazier, more vague and more confused. He is almost marooned in the moment, something even more apparent in cases of severe amnestic difficulties and of senility, in which the only link with the present is the dim distant and practically irrelevant past.

In the second case the same general attributes of behavior will be noted, but the interest will center about the appearance of retrogressive amnestic difficulties and confabulation along with the more severe memory impairment.

CASE 2.—G. E., a chronic alcohol addict aged 50, was hospitalized in February 1938, fourteen months before the studies were started. Marked forgetfulness was noted for several months before admission, when he was drinking even more heavily than usual. He began to neglect his appearance, cleanliness and nutrition, and when finally he became noisy and talked to himself commitment became necessary. He had received a fifth grade parochial school education. Unmarried, he had lived in boarding houses since his mother's death, about ten years before admission, and had supported himself by selling classified advertising. Earlier in his life he had worked as a machinist at a shipyard. At the time of admission he suffered from peripheral neuritis and was completely disoriented.

During the period of observation G. E.'s behavior was similar to that of O. S. He appeared well adjusted on casual examination but did little except sit, rarely conversing. He displayed initiative only in his desire to attend occupational therapy courses, where he would saw boards at random but would demonstrate the handiwork of others as his own productions. He would also frequently peruse the newspapers but could never tell anything of the news, insisting that he was interested only in the obituaries. Orientation to time was maintained by noting the date from day to day and holding fast to the date of his admission. Familiar with the major features of hospital routine, he knew on which days he bathed and shaved and when visitors might come. When transferred to a different section of the hospital to facilitate observation, he readily found his way about in the new surroundings. Major events, such as the transfer from one building to another, were remembered, as were the names of a few attendants and physicians. Short durations of time were correctly appreciated, and he knew the approximate time of day and the lengths of interviews, but periods extending overnight were estimated erroneously. On the basis of these capacities, his behavior was in no way remarkable for a patient in a chronic disease ward of a state hospital.

Conversation rapidly revealed the flimsiness of the shell of normality. The friendly greeting, followed by a few stereotyped remarks, ended his spontaneous talk. The good spirits which were often present vanished when precise answers were required. He explained that he had been brought to the hospital after an injury to his leg at the shipyard, an event which had occurred over ten years before. He said that his mother had been dead for a year or two (actually ten or eleven) and that his father was still alive (he had been dead for seven years). A day after the transfer to a different building he said that it had been over a week, and the recollection of his former residence was already hazy. It was clear that he recalled little of recent happenings, and his recollection of the past ten years or more was faulty. Memory for the past years had not been oblit-

erated, for it was found that in response to direct questions he could recall a good deal, including the address of the boarding house in which he had lived for but a few weeks prior to admission. It was that the events of the past years were jumbled without regard to the time of actual occurrence. When the discrepancy between his explanation of his hospitalization and his knowledge that he had been selling advertising for ten years was called to his attention, he simply modified the explanation, which had become a fundamental feature of his orientation, by saying that he believed that he had returned to the shipyard shortly before admission. On the following day he would revert to the simpler explanation. Similarly, he said that he had worked in the shipyard during the first World War, which he then allocated as of 1898, noting no discrepancy until asked how old he had been at the time.

G. E. rarely admitted that he could not remember but gave vague statements which he hoped would suffice, stalling for the interviewer to ask a leading question. At other times he made definite statements which were totally fallacious but were difficult for one to deny without insulting him. Usually his answers sounded plausible and required careful checking. He insisted that he was perfectly well, though he might have been delirious on admission because of his accident. He protected his weakness, and there was reason to believe that he was not totally devoid of insight. He never brought up the question of discharge, except as a counterattack when cornered by questions which he could not answer.

Test situations similar to those employed in the first case were used to determine the range of capacities. The results clearly indicate the greater severity of the difficulty in dealing with time-allocated material and also hint that reflective ability was not fully intact. The Binet test, after exclusion of items clearly dependent on memory, gave a mental age of 11 years, and failure on the vocabulary test at the 10 year level is indicative, though not conclusive, evidence that intelligence had never been higher.[12] The Kohs block test gave him a mental age of 10½ years; the Healy completion test, 11½ years; the Porteus mazes were completed even better than by O. S. The results of still other performance tests conflicted with the implication drawn from these studies that reflective ability was fairly intact, for on the feature profile test[13] and the two figure form board,[13] tests on which O. S. had done very well, this patient fell far below his mental age level. As clearcut differences in the demands placed by the various tests cannot be ascertained, the suggestion can only be accepted that his analytic and synthetic capacities were not fully intact.

Tests with material offered in sequence showed conclusively that capacity to utilize the transient was more severely impaired than in the first patient. When three pictures were shown successively only the third could be recalled spontaneously; the first could be recalled with definite hints, and the second could be recognized only when seen again. Similarly, he could recollect only meager fragments of the three Binet fables when aided and, when pressed further, filled the gaps by the creation of detail, an indication of one of the sources of confabulation. With the comic strip shown in a succession of separate pictures, only a few fragments, without any appreciation of the meaning, were recalled. The drawing of

12. Babcock, H.: An Experiment in the Measurement of Mental Deterioration, Arch. Psychol., 1930, no. 117.

13. Pintner, R., and Patterson, D. G.: A Scale of Performance Tests, New York, D. Appleton and Company, 1923.

the abstract-labeled pictures brought immediate distortion (figure *B*). It is seen not only that the ability to utilize material from the past is more limited than in the first patient but that distortions according to his preconceptions occur far more rapidly.

Two sources of error which lead to involuntary "confabulation" are noticeable in the test situations and general conversation in this case. Indications of these errors can be noted in retrospect in the first patient, and indeed are present in normal persons, as shown by Bartlett.[8] All persons tend to retain essentials and when remembering to fill the gaps according to preconceptions of diverse origins. When recall is deficient such distortions occur more rapidly and are unavoidable, particularly when insight is lacking. Present in the drawings and interpretations of comic strips by O. S., this type of error pervades most of the conversational efforts of this patient. A picture of two men conversing, with a mule in the background, rapidly becomes a picture of two men arguing how to pack a mule. A second source of error lies in the inability to hold impressions discrete. It was noted when O. S. mixed up the two comic strips. After a month's residence in a ward, G. E. still spoke of going upstairs to bed and of a pool table in the dayroom, both features of the building in which he had lived for over a year. The overlap of memories may have several origins and is probably related to the inability to select actively the desired image, as noted by Pick and Grünthal, and to the absence of recollection of events which fill the time between occurrences.

An understanding of the nature of the retroactive amnestic difficulty is essential for the discussion of the most blatant type of "confabulation." In the first case events which had occurred prior to the asphyxiation could be recalled accurately, but only in response to questioning; the return of elaboration in talking of the past after recovery suggested that the past had not been spontaneously available. In the case of G. E. the isolation of material from his former life is marked; direct questioning is essential to effect recollection, and the items when recalled are disconnected from one another and from the sequence of his life. He can be made to tell the names of the landladies and the length of his residence in several boarding houses subsequent to his mother's death, which does not prevent him from saying that his mother had died but a year or two before the interview. Numerous such discrepancies can be noted. It is not that the past years have disappeared completely, but that the past consists only of a jumble of isolated happenings. Isolated events have no time relation because they are not correlated with other events. The memories appear by associations evoked by a question rather than by reflective selection of the appropriate. Moreover, it seems possible that the more firmly coherent past of his youth, because it is more readily

available, may seem more recent than the actually proximate past. The difference between the first patient's difficulty, in which external stimulation was necessary to promote recollection, and this patient's disturbance, in which the past is disconnected, does not seem great.

Attempts to explain something on the basis of the inconstant background of the faulty memory will usually be erroneous and confabulatory. A person is dependent on the integrity of his memory to understand the interrelations of the past as well as to understand the present. The use of erroneous points of departure, such as G. E.'s explanation of the reason for his hospitalization, only multiplies the errors. It is only his ability to retain orientation so far as he knows that he is in a hospital and the length of his stay which prevents him from falling into far more obvious errors, as will be seen when the third case is described.

The sources of errors usually termed confabulation, which have been described, seem inherent consequences of the memory deficit. A further impetus to confabulation arises from the need to avoid anxiety. Although memory difficulties have been ascribed to the apathy,[1] it was clear that questions which forced recognition of his deficiency produced severe emotional stress. His hands would tremble; his forehead would break out with perspiration, and he would become angry and uncooperative if unable to sidetrack the examiner. Williams and Rupp[14] noted that several of their patients had insight before they would admit it, and continued confabulating. G. E. may have had an inkling of his difficulties, which he strove to prevent from becoming apparent to himself as well as to the examiner. Instead of admitting ignorance, he would offer a casual confabulated answer.

The intact capacities are of interest, for not only do they afford the basis for the semblance of normal behavior, but their misuse of what remains available to fill the gaps helps create the picture of the disturbance. Habitual activities and modes of reacting to customary situation remain, as in most persons with limited damage to the brain. Although transient events which impinge on him pass without being connected to the mass of his experience, a few linkages are made, only to be distorted when recalled. His surroundings, which are relatively nontransitory, afford a gross frame of reference into which experiences can be placed. The repetitive events which take place against this background are utilized with a proper concept of time, even though appreciation of the passage of time is faulty. The relatively intact capacity to think reflectively permits him to make a moderately sensible use of whatever he can muster, but little is available that is free of distortion.

14. Williams, H. W., and Rupp, C.: Observations on Confabulation, Am. J. Psychiat. **95**:395 (Sept.) 1938.

The difficulties imposed by the deficit are complex. Even more than with the first patient, occurrences pass him by without being connected sequentially or with the past, which is less available, leaving them unavailable for recall. The few transient events which are retained are, in turn, distorted when he wishes to use them, because the gaps must be filled in, the time setting is lacking and the events are blended together. When he needs to go back to his earlier life for data, little reappears spontaneously, except perhaps the very remote past. When something in his surroundings arouses an association with his past, it is a passive, unselected and disconnected recollection. The use of such recollections devoid of time setting gives rise to contradictions between themselves and with the sequence of his life. Lack of recognition of the erroneous point of departure in his past permits him to talk freely at times if unimpeded by correction, but the productions are composites of errors. The relatively intact reflection turns out material which is erroneous because the few transient recent events which he uses are distorted and the past appears unselected and without appropriate time setting. The patient's belief in his normality and the efforts to preserve his equanimity contribute unchecked errors and more or less conscious confabulation.

The third case, an example of the most severe amnestic disturbances, with inability to grasp the transient, which has produced total disorientation, and inability to evoke the past, which has made recent years inaccessible, culminates the series. Considerable habitual activity can still be carried on, but general intellectual deterioration differentiates this case from the preceding.

C. S., a 56 year old man with severe chronic alcoholism, was admitted to the Springfield State Hospital in December 1938, after he had been suffering from delirium tremens for at least four days. A history of total neglect of his person for several months prior to admission suggests that deterioration had antedated the delirium. He had always been an irresponsible person, who had pursued many occupations during his life. He had but a fifth grade education but was said to have been fairly intelligent. On admission there were dysarthria, coarse nystagmus on lateral gaze and a positive Romberg sign, the result of involvement of the posterior column rather than peripheral neuritis.

Three months after admission, when the studies were started, the patient was still totally disoriented for time and place. Occasionally he recognized that he did not know where he was, but the answer given him was immediately forgotten. Orientation shifted rapidly; most often he believed himself in a firehouse awaiting an examination or visiting some one on his way home from a trip. He either had just arrived or, occasionally, had slept overnight. The date varied between 1908 and 1928, but he always insisted that he was less than 30 years old. Inconsistency of responses made no impression on him even when called to his attention. Within a few minutes he would say that he did not know where his wife was, as they had separated, that she was in a state hospital or that she was dead —all true at some time in his life.

In contrast to the condition presented by the first 2 patients, his disorientation was obvious, for remarks were not even approximately appropriate. He was unable to find his way about and would act as if he had just arrived and the attendants whom he saw daily were strangers. He recognized the name of the hospital as a "place for crazy people," but this had no effect, as it was immediately forgotten. The brevity of his memory made planned behavior impossible, as he would forget what he was to do while on his way to do it.

Confabulation was prominent at all times but seemed solely dependent on his faulty and shifting orientation, as errors could not arise from distortion of material, as in the case of G. E., for no recent occurrences were available to him. He talked as if it were 1908 and he were a bartender, or 1912 and he were on a fishing trip. The surroundings were not grasped properly and did not affect his orientative set.

Usually he sat in the ward totally inactive, but on several occasions when he based his conversation on an erroneous point of departure he became talkative. The relation between orientation and activity appears worth noting. The most appropriate behavior, as understood in the patient's own terms, occurred on one occasion, which lasted for several days, when he believed that he knew where he was and acted accordingly. Another patient, to tease him, told him that he was about to be hanged and indicated some construction work in the courtyard as the erection of the gallows. Immediately the apathy disappeared, and for several days he paced the ward in agitated fashion, asking whom he had killed, writing farewell notes to his parents and disposing of bank accounts which he had possessed many years before. No amount of reassurance altered the situation, for it was immediately forgotten, whereas the basic orientating idea remained. It seemed as if all the puzzling features of his environment, of which he must have been dimly aware, were suddenly illuminated. The orientation pervaded his entire behavior, with neglect of everything told him, which, of course, could not be recalled. It was clear that he was capable of appropriate affect and could initiate activity when he had a foundation on which he could act. When reassurance failed, transfer to a different ward immediately changed his orientation; the idea that he was about to be hanged vanished, and with it all activity. He again sat awaiting an examination in the firehouse.

The test situations revealed what his behavior suggested; he was deteriorated in all spheres. The brevity of his memory made the Binet test worthless, but attention could be kept focused on performance tests. Inability to do anything with the feature profile test, the Healy completion test and the Kohs blocks indicated severe deterioration even if intelligence had formerly been very low. In drawing a face he placed features incorrectly, and his sketch of a house might have been anything at all. He could define only the simplest words.

Demands which required recall showed a performance totally different from that of the first 2 patients. When asked to repeat the Binet fire story, he simply started to talk about a fire in Baltimore. Three pictures shown in succession were not even recognized when shown for a second time after the lapse of a few minutes. The defects had spread to perception, for interpretations of pictures were faulty even while he was looking at them. Even direct copying of pictures was inaccurate. When shown a square, a triangle and a circle in rapid succession and asked to draw what he had seen, a task which offered no difficulties to the first 2 patients, he drew a crude picture of a man, with the circle as the head, the triangle as the body and the square changed into legs (figure *C*). It seems

clear that numerous sensorial deficits can be demonstrated in this patient which have little specific relation to the nature of the amnestic difficulty; yet it is from cases of this type that conclusions have not infrequently been drawn.

Although the deficits are more extreme here than those in the preceding cases, the transition can still be noted. With the inability to recall any recent occurrence, even the environment is insufficiently stable to be grasped. There are no recent events which can serve as a basis for orientation, to which in turn transient occurrences could be linked, as in the case of G. E. The rapid forgetting precludes knowledge of how he reached the present moment. Transient events summon only irrelevant associations from the past, which then form the basis for his orientation, shifting from moment to moment.

The post-traumatic impairment, because of the total inability to recall recent occurrences, blends with the retrogressive difficulty, and the patient mentions nothing belonging to the past ten or more years. In contrast to the case of G. E., in which questions could revive isolated recollections, here many years seem to be wiped out. It is not a clearcut loss for a definite period, since memory for the more remote past is fragmented and is not utilized with proper appreciation of the time relations. Again, as in the case of G. E., it is the hooking up of the moment with something revived from any portion of the past.

With inability to use anything which has just happened or material from recent years, the moment can be linked only with something from his youth, and it will of necessity be handled in a confabulatory fashion. Added to these handicaps is the deterioration in the handling of material irrespective of recall. Although a memory deficit of the extent seen in this patient might well interfere with normal perception by the failure to provide pertinent associations necessary for comprehension, it is a definite impression that the deterioration goes beyond dependency on recall and, together with the diffuse neurologic signs, indicates generalized cortical destruction.

The sources of the confabulation appear to be simpler than in the case of G. E. The patient being totally devoid of insight, there is no need to avoid anxiety. Errors in recall of recent items do not occur, for nothing recent is recalled. The confabulations are the result of attempts to understand the moment in terms of the associations from the past, with disregard of the gap in the time. When the patient is talking of the past without reference to the present, confabulations arise because of the inability to select the pertinent memories, and episodes from different periods of his life are placed in proximity and connected. Here, again, is an illustration of how the cause of the manifestations, as well as the manifestations themselves, varies with the severity of the syndrome.

Relatively little can be learned from a patient with such severe deficits except by comparison with the other patients, for the diffuseness of the deterioration does not offer stable ground on which attempts at analysis can be based. The loss of orientating features, in contrast to their presence in the preceding cases, has in itself produced a striking change, and nothing but complete confabulation can be expected. A similar feature of differentiation can be noted in senile patients. An aged person may talk only of his childhood and recollect little of recent events but is often not obviously psychotic as long as sufficient of what is going on about him can be recalled to retain orientation. When the stage is reached when he talks no longer about his childhood, but as if he were in his childhood, his difficulties become obvious and he needs to be cared for.

A patient with amnestic difficulties of the degree shown by C. S. has lost all time sense, for when understanding depends only on associations with the dim past there can be no sequence of events. He is a prey to whatever is aroused by the situation, for linkages between events can neither be made nor regained. The resultant picture is one of thoroughgoing dilapidation, far different from that in the first case presented.

COMMENT

The description of the alterations of the syndrome from case to case with the increasing severity of the amnestic deficit has sought to clarify the interrelations and meanings of the various manifestations. The disturbance of time sense, the loss of spontaneity and the passivity, the difficulties in appreciating the meanings of situations, the confabulations and the disorientation appear as necessary consequences of the inability to utilize the transient occurrences once they have gone by and of the amnestic difficulties which extend retrogressively. The division of the amnestic deficit into retrogressive and post-traumatic loss in the description of the cases appears arbitrary, particularly in view of the consistent increase in involvement of both types from case to case. It is a division which has caused considerable concern to investigators, and resolution of the division appears to lead to a more thorough understanding of the nature of the amnestic difficulty.

It has been indicated by numerous observers that the retention difficulty is not proportionate to the severity of the memory impairment and that it does not explain the retrogressive loss. On the other hand, it has been shown [1] that the last impression seems to obliterate the preceding ones. Once an occurrence has passed from the present, it must be regained from amid the horde of occurrences and associations termed the past. From the present study it appears necessary to recognize that the amnestic deficit is concerned with the inability or disability to regain material which is past in the sense of having

been followed by subsequent impressions. The patient must be capable of placing himself in the proper setting imaginatively or of leading into the trend of associations with which the desired recollection is connected. For all normal behavior the proper associations from the past must reappear more or less spontaneously, and for reflective behavior and planning the person must be capable of selecting the proper recollection from among a number of alternatives. This is not the same as inability to shift from a single line of thinking, as suggested by Grünthal,[5] though it is a clarification of the same general principle. The first 2 patients were able to alter the trend of their thinking when the material was independent of recall. Nor is it the same as saying that the patients cannot alter their orientative set (*Einstellung*), for even the third patient could alter his orientation rapidly.

The relative inaccessibility of the past, personal and impersonal, in that there is difficulty in finding the path to it, explains the retroactive deficits. In the first case questions were answered correctly, but there was no elaboration, for collateral material did not become available; in the second case retrogressive recollections were evoked with outside aid but remained disconnected from one another, which caused numerous errors; in the third case the recall was purely passive and many years were unavailable. In all except the third case the memories were available if the patient was directed toward them, and even in patients similar to the third Williams and Rupp[14] noted that with improvement periods which were not available returned. It is not a question of the wiping out of the memories from before the time of the injury to the brain.

The handling of material which occurred after the injury to the brain is worse than that of the retrogressive material. This has frequently been noted under the term "loss of recent memory." Whereas the impressions prior to injury had been perceived with sequential connections and blended into the mass of the patient's experience by numerous associative connections, events after the injury impinge on a person in whom the past does not arise to associate with the new. The person is incapable of linking things sequentially or with the mass of his experience. The impression remains more or less isolated and unconnected and therefore can be recalled with difficulty or not at all. In turn, it does not supply a foundation for the subsequent impression, for it is rarely available without outside guidance. In contrast to the retrogressive material, the post-traumatic events are not regained after recovery, never having been completely perceived and integrated. The difficulty in utilizing the past, therefore, has a different effect on new material than on events already incorporated as a part of the person's past at the time of the damage to the brain. The latter is recalled with difficulty, causing retrogressive defects, whereas the former is never

integrated properly and is even less available for recall and utilization. Retention can be said to be faulty, but the difficulty lies in the foundation on which the new impression is placed.

SUMMARY

The amnestic syndrome, in three grades of severity but limited to patients in whom the memory deficit was the predominant feature and not a part of a more sweeping disorganization, is described. Attention is called to the variation in the behavioral pattern, with increasing impairment in utilization of material which had been previously experienced. In the first patient the inability to connect the moment to what came before and the paucity of material for inner stimulation led to loss of initiative, apathy, passivity and disturbance of the grasp of time relations. The forerunners of confabulation and retrogressive defects could be noted. In the second patient the disturbance in use of transient and sequential material was more obvious and gave rise to distortions of recollection; events prior to the damage to the brain could be recalled with outside aid but remained isolated and without proper temporal allocation, and this was the major source of the confabulation. The third patient, unable to recollect after a few moments, was totally disoriented and unable to regain anything from recent years; all utterances were based on faulty orientation and were confabulatory.

The major manifestations of the syndrome—passivity, confabulation, disorientation, loss of "time sense" and difficulties in altering the orientative set (*Einstellungsstörung*)—appear as consequences of the disruption of integrated behavior when the past is not freely available. The hypothesis is offered that both retrogressive deficits and inability to deal with transient events can be understood as parts of the difficulty in freely evoking past experiences. Utilization of post-traumatic events is most seriously disturbed because they are not met by the background of past experience essential to full perception.

FACTORS AFFECTING CHANGES PRODUCED IN ELECTROENCEPHALOGRAM BY STANDARDIZED HYPERVENTILATION

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During the summer of 1940 electroencephalograms were recorded, as part of a program of physiologic and psychologic testing, on approximately 450 aircraft pilots.[1] One objective was to determine the incidence (if any) of cerebral dysrhythmias. It is well known that voluntary hyperventilation often precipitates both petit mal attacks and their accompanying electrical patterns (Gibbs, Lennox and Gibbs[2]). Hyperventilation is employed as an adjunct to diagnostic procedure in many hospital electroencephalographic laboratories. We therefore included a three minute period of maximal voluntary hyperventilation as part of our routine test. We immediately confirmed the already familiar observation that many presumably normal persons show more or less prominent delta waves, or at least waves in the 4 to 8 cycle band, as a result of such hyperventilation. It seemed possible that the amount of such slow wave activity might serve as a useful index of "cerebral instability" and have some predictive value in regard to

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Read at the Sixty-Seventh Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 10, 1941.

An abstract of this paper was read at the meeting of the American Physiological Society, April 19, 1941 (Davis, H., and Wallace, W. McL.: Am. J. Physiol. **133**:P258, 1941).

1. In 1939 the Civil Aeronautics Authority initiated a large scale program of research in the selection and training of aircraft pilots. Funds provided by the Civil Aeronautics Authority have been administered by the National Research Council, and the two organizations concerned have shared the direction of the research program. The observations here described as made during the summer of 1940 represent part of one investigation carried on under these auspices.

2. Gibbs, E. L.; Lennox, W. G., and Gibbs, F. A.: Variations of Carbon Dioxide Content of Blood in Epilepsy, Arch. Neurol. & Psychiat. **43**:223 (Feb.) 1940. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Dysrhythmias of Epilepsy: Measures for Their Control, ibid. **39**:298 (Feb.) 1938.

success or failure in aviation. To test this hypothesis we undertook to standardize the hyperventilation test, so that the willing and enthusiastic candidate or the man with large vital capacity would not subject himself to a more rigorous test than the lazy or hesitant breather or the man with a relatively small chest. We chose 15 breaths per minute as the standard rate of breathing and 20 cc. per pound (44 cc. per kilogram) of body weight as the standard tidal air.[3] The pulmonary ventilation was therefore 300 cc. per pound (660 cc. per kilogram) per minute, or 45 liters per minute for a 150 pound (68 Kg.) man. Most, but by no means all, of the subjects could attain this rate of ventilation. To measure the tidal air and thus enable us to instruct the subject to breathe more or less deeply as required, we recorded the respiration by means of a special Sanborn metabolism machine with low resistance to the flow of the respired air.

Comparisons of repeated tests on a given subject and the performance of groups of men under different conditions showed the following characteristics: 1. There was somewhat less tendency for our subjects to show delta waves in the electroencephalogram when breathing air from the metabolism machine at our prescribed rate than when hyperventilating without the machine with no restriction. 2. When the machine was filled with oxygen there was far less tendency for delta activity to develop than when the machine was filled with air. 3. Enrichment of the air in the machine with 800 cc. of oxygen, to provide an average oxygen content of about 20 per cent during the three minute test, yielded less delta activity than filling the machine with air but more than filling it with oxygen.

A series of more elaborate experiments was therefore undertaken in the department of physiology of the Harvard Medical School to determine what further standardization of the hyperventilation test might be required to render it useful for the determination of individual differences in the "stability" of the central nervous system as judged by the appearance of slow waves in the electroencephalogram.

APPARATUS AND METHODS

Electroencephalograms were recorded by means of a six channel ink-writing oscillograph (Grass). Solder electrodes were placed on the left frontal, left precentral and left occipital areas and a reference electrode on the left ear lobe. The subject lay (with eyes closed) on a cot and breathed in a rhythm set by a metronome into a Collins metabolism machine equipped with Bailey valves. With

3. The convenient practical rule followed was "1 mm. excursion of the drum of the Sanborn metabolism apparatus per pound of body weight" (2 mm. per kilogram).

a little practice the 4 men on whom most of the present observations were made maintained an even pulmonary ventilation within a few per cent of the arbitrary standard except during periods of great delta activity, as noted below (fig. 2). The spirometer was filled with oxygen or with air enriched with 800 cc. of oxygen. In several experiments the oxygen absorbed was continuously replaced, but the results did not differ significantly from those obtained with the originally enriched air.

Just before and just after each period of hyperventilation 0.3 to 0.5 cc. of cutaneous blood was obtained by incision of the finger, collected under oil and oxalated according to the procedure of Shock and Hastings.[4] As far as chemical constitution is concerned, such blood is indistinguishable from arterial blood (Drucher and Cullen[5]; Foster[6]). These blood samples were analyzed in duplicate by the method of these authors, and information was obtained on the following factors: hematocrit reading, serum p_H at 38 C. and whole blood carbon dioxide content. From these data carbon dioxide tension and serum bicarbonate were calculated, using the Henderson-Hasselbalch equation. Whole blood carbon dioxide values were converted to serum values by the nomogram of Van Slyke and Sendroy.[7] Blood sugar, which proved to be an important variable, was determined on the same samples by the micromethod of Folin,[8] using laked blood filtrates.

Three channels of the electroencephalograph were connected to the left frontal, the precentral and the occipital lead, respectively (reference electrode on the ear). The sensitivity of these three channels was adjusted to 1 mm. for 10 microvolts. The three remaining channels were all connected to the left precentral lead and a filter was inserted in each circuit, tuned broadly[9] to 7, 5 and 2.8, or in some experiments to 3.5 cycles, respectively. The sensitivity of the tuned circuits was approximately 1 mm. for 5 microvolts for sine waves at the frequency to which the filter was tuned. The filtered circuits greatly facilitate the detection of the slow waves of various frequencies that appear during hyperventilation (fig. 3). As an arbitrary but useful method of quantitating the changes in the record, we counted for each thirty second period in each filtered record the number of waves that attained or surpassed a given amplitude (6 mm.) on the record. The trends were similar for all filters, but the increase appeared earliest and rose to greatest value for the 7 cycle filter and was least for the 2.8 cycle filter. The total three minute count for the 5 cycle filter is a convenient single index, and the results to be presented are based primarily on these counts (the "5 cycle count").

We measured also a modified "delta index" (Hoagland, Cameron and Rubin[10]). The ten second period containing the greatest delta activity was selected by

4. Shock, N. W., and Hastings, A. B.: J. Biol. Chem. **104**:585, 1934.

5. Drucher, P., and Cullen, G. E.: J. Biol. Chem. **64**:221, 1925.

6. Foster, G. L.: J. Biol. Chem. **55**:291, 1923.

7. Van Slyke, D. E., and Sendroy, J.: J. Biol. Chem. **79**:781, 1928.

8. Folin, O.: J. Biol. Chem. **77**:421, 1928.

9. For all except the 2.8 cycle filter, the ratio of the frequency at which the amplitude is one-half that of the amplitude of the peak frequency to the amplitude of the peak frequency is 1.55; that is,

$$\frac{\text{Frequency at which amplitude is } \frac{1}{2} \text{ maximum}}{\text{Frequency at which amplitude is maximum}} = 1.55.$$

The corresponding ratio for the 2.8 cycle filter is 2.5.

10. Hoagland, H.; Cameron, D. E., and Rubin, M. A.: Am. J. Psychiat **94**:183, 1937.

inspection, and on the unfiltered precentral record the length of line was measured with a cartographer's wheel, all waves the wavelength of which was one-fifth second or less being disregarded. The result was expressed as percentage excess length over 30 cm. (the length of record corresponding to ten seconds) and was designated as the "maximum delta index."

RESULTS

A. Constancy of Changes in p_H and pCO_2 Produced by Hyperventilation.—The values for p_H and pCO_2 measured before periods of hyperventilation on a given subject on a given day varied at most by 0.22 unit and by 2.5 mm. of mercury, respectively. From day to day and from subject to subject the variations were slightly greater, but nearly all of the values lay within the normal range defined by Shock and Hastings.[4] The pulmonary ventilation, standardized as already described, lay between 285 and 320 cc. per pound (627 and 704 cc. per kilogram) per minute in nearly all cases. Occasionally the subject failed to maintain his full depth of breathing throughout the third minute. The tendency to "slack off" was nearly always associated with the appearance of trains of delta waves in the electroencephalogram, but the subjects regularly responded to instructions to breathe more deeply and the total ventilation for the three minute period was only slightly below standard.

In spite of the standardization of the hyperventilation, the values for p_H and pCO_2 taken immediately after hyperventilation varied considerably. One important cause for the variation was the different degree of vasoconstriction encountered and the consequent prolongation (up to two minutes) of the time required to collect the blood sample. During the collection the acid-base displacement of the blood was of course returning toward normal. In 1 subject (J. H.) the vasoconstriction was pronounced in three experiments. The average increase in p_H in seven tests in which vasoconstriction was specifically noted was 0.10 unit and the diminution in pCO_2 was 10.6 mm. of mercury. In three other tests (in two of which oxygen was breathed) the subject bled freely. The average increase in p_H in these three tests was 0.19 unit and the fall in pCO_2 was 17.1 mm. of mercury. Four other subjects who bled fairly well showed an average increase in p_H (nineteen tests) of 0.17 unit (extremes, 0.125 and 0.23 units) and a fall in pCO_2 of 15.3 mm. of mercury (extremes, 11.9 and 20.5 mm.). The subject who bled most freely showed a consistent change (three tests) of about 0.19 p_H unit and 17.2 mm. of mercury. In a few other tests the subjects continued hyperventilation at a somewhat reduced rate (150 to 200 cc. per pound [330 to 440 cc. per kilogram] per minute). The measured changes in p_H and carbon dioxide tension approximated the values obtained in the previous tests, in which the bleeding had been most rapid.

We conclude that variations in vasoconstriction and consequent speed of bleeding prevent accurate determination of the p_H and pCO_2 of finger blood at the end of the three minutes of hyperventilation. Our measured changes represent minimum rather than actual values, and the best approximation seems to be to assume that the changes produced by the standard amount of hyperventilation are constant and a little greater than the average for the tests in which bleeding was freest, say an increase in p_H of 0.20 unit and a fall in carbon dioxide tension of 18 mm. of mercury.

Comparison of the measured changes in p_H and pCO_2 with changes in the electroencephalogram reveals no clear correlation, except that the subject who showed most vasoconstriction tended to have the greatest

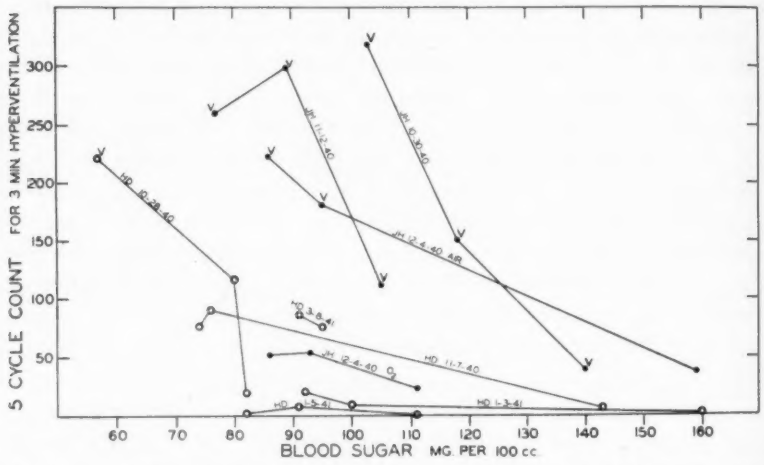

Fig. 1.—To determine the 5 cycle count, waves exceeding an arbitrary maximum amplitude (6 mm.) in the precentral electroencephalographic record, taken through a broadly tuned 5 cycle filter, are counted for three minutes of hyperventilation, which was standardized at the rate of about 300 cc. per pound (660 cc. per kilogram) of body weight per minute. (In the experiment on J. H., 11/12/40, the ventilation was 345 cc. per pound [760 cc. per kilogram] per minute.) For further details see the text and tables 1 and 2.

In all of the tests designated by *V* there was definite evidence of peripheral vasoconstriction during or after the hyperventilation. The subject bled poorly when pricked or complained of feeling chilly. Often he looked pale. It is evident that the observed vasoconstriction tends to be related to the high 5 cycle counts.

increases in delta index when the measured changes in p_H and pCO_2 were the least. In other words, the change in the electroencephalogram correlated with the amount of vasoconstriction rather than with the observed changes in p_H and carbon dioxide tension (fig. 1).

B. Reproducibility of Electroencephalographic Changes in Response to Standard Hyperventilation.—Repeated tests on a given subject on the same day at intervals of from fifteen minutes to three and a half hours, other conditions remaining constant, produced fairly constant increases in the 5 cycle wave count and in the maximum delta index. Table 1 illustrates a series of such comparisons. (The values for the last pair of tests on W. W. are not comparable with his first pair, as the spirometer was filled with pure oxygen instead of air enriched with only 800 cc. of oxygen.) This last pair of tests and the tests on W. W. on Feb. 8, 1941 at 2:01 and 2:31 p. m. (table 2) represent the greatest divergences in any pair of matched tests we have performed on the same day. Frequently the first test performed in the morning, other

TABLE 1.—*Reproducibility of the Effect of Hyperventilation*

Subject	Date	Time	Mixture	Ventilation, Cc./Lb. Min.*	Blood Sugar, Mg. per 100 Cc.	5 Cycle Count	δ Index (Maximum)
J. H.	11/12/40	11:12 a.m.	Air + 800 cc. O_2	345 ↓ ↓	89	298	97
		11:30 a.m.	Air + 800 cc. O_2	333 ↓	..	262	90
		2:16 p.m.	Air + 800 cc. O_2	345 ↓	77	200	100
H. D.	11/7/40	11:05 a.m.	Air + 800 cc. O_2	311	76	91	20
		11:52 a.m.	Air + 800 cc. O_2	311 ↓	..	65	17
		2:34 p.m.	Air + 800 cc. O_2	304 ↓	74	76	14
	3/6/41	11:27 a.m.	Air + 800 cc. O_2	304 ↓	99	85	19
		11:52 a.m.	Air with O_2 replenished	307 ↓	87	93	13
	3/8/41	10:00 a.m.	Air with O_2 replenished	305	95	76	20
		11:27 a.m.	Air with O_2 replenished	309	91	86	18
W. W.	3/8/41	10:18 a.m.	Air with O_2 replenished	302 ↓	<90	221	30
		11:05 a.m.	Air with O_2 replenished	300 ↓	83	224	22
		9:32 a.m.	O_2	302	89	150	22
		11:48 a.m.	O_2	300	89	89	16

* A vertical arrow directed downward indicates that the pulmonary ventilation fell off somewhat during the third minute; two arrows indicate marked falling off. Where arrows are present, measurement of ventilation is based on the first two minutes of the test.

things being equal, showed a somewhat greater change in the electroencephalogram than did subsequent tests. The first two pairs in table 1 show such a difference, but it does not always appear and may be a spurious effect (cf. also figure 1).

Individual differences among the 3 subjects appear clearly in table 1 and figure 1 and are fairly consistent. Unfortunately, the day to day reproducibility is not so good as the data on H. D. in table 1 suggest. On another day H. D. showed a 5 cycle count of only 17 waves and a delta index of 8, and on still another day, a 5 cycle count of 5 waves and a delta index of 2 (table 2). The conditions of these two tests were in all respects similar to those listed in table 1. Such day to day variability is less than the interindividual variation between H. D. and

TABLE 2.—*Effects of Ingestion of Sodium Bicarbonate ($NaHCO_3$) and Ammonium Chloride (NH_4Cl) on Hyperventilation with Oxygen and with Air*

Subject	Date	Time	Mixture	Ventilation, Cc./Lb. Min.	Blood Sugar, Mg. per 100 Cc.	5 Cycle Count	δ Index (Maximum)	p_H Before	pCO_2 Before, Mm.	Serum $[BHCO_3]$ mM/L.
H. D.	1/ 3/41	10:48 a.m.	Air	305	92	21	8	7.41	40.5	25.1
		12:39 p.m.	O_2	296	91	7	0	7.41	38.5	23.9
			Ingested 20 Gm. $NaHCO_3$							
		1:54 p.m.	Air	307	100	9	0	7.47	41.0	29.0
		2:33 p.m.	O_2	305	87	0	0	7.47	39.5	28.0
	1/ 5/41	10:20 a.m.	Air	298	91	8	2	7.45	36.6	24.8
		10:55 a.m.	O_2	296	88	3	0	7.43	37.5	24.1
			Ingested 15 Gm. NH_4Cl							
		1:32 p.m.	Air	298	82	2	1	7.29	37.5	17.1
		2:02 p.m.	O_2	304	87	9	3	7.29	33.0	15.4
	3/6/41	10:55 a.m.	O_2	288	93	41	14	....	....	....
		11:27 a.m.	Air	288↓	99	85	19	....	....	....
	3/8/41	11:27 a.m.	Air	309	91	86	18	....	....	....
		12:05 p.m.	O_2	312	92	40	10	....	....	....
J. H.	12/4/40	9:05 a.m.	Air	304↓	95	181	80	7.40	41.8	25.0
		9:35 a.m.	O_2	302	93	54	13	7.38	44.2	25.2
			Ingested 20 Gm. $NaHCO_3$							
		10:50 a.m.	Air	300↓	86	223	50	7.49	39.0	28.5
		11:20 a.m.	O_2	310	..	52	9	7.45	45.0	30.0
	1/7/41	9:58 a.m.	Air	344	93	16	3	7.40	43.0	26.1
		10:40 a.m.	O_2	333↓	87	11	0	7.40	42.3	25.1
			Ingested 12 Gm. NH_4Cl (vomited at 12:55); little effect on p_H							
		1:31 p.m.	Air	326	100	18	1	7.38	39.5	22.5
		2:16 p.m.	O_2	304	84	10	3	7.39	41.0	23.9
W. W.	2/8/41	10:37 a.m.	Air	317↓	78	40	2	7.43	35.2	22.6
		11:07 a.m.	O_2	300	..	24	0	....	....	....
			Ingested 12 Gm. NH_4Cl							
		1:22 p.m.	Air	300	82	24	0	7.26	35.2	15.5
		2:01 p.m.	O_2	314	..	56	1	....	....	....
		2:31 p.m.	O_2	310	81	2	0	7.28	32.2	14.6
	2/15/41	9:18 a.m.	Air	314	80	170	4	7.43	39.0	25.0
		9:55 a.m.	O_2	300	82	12	0	7.43	39.0	25.1
			Ingested 20 Gm. $NaHCO_3$ (diarrhea)							
		11:22 a.m.	Air	319↑	91	13	2	7.48	40.0	29.2
		12:00 a.m.	Air	317	94	3	0	7.45	41.0	28.0
	3/8/41	9:32 a.m.	O_2	302	89	150	22	....	....	....
		10:18 a.m.	Air	302↓	<90	221	30	....	....	....
		11:05 a.m.	Air	300↓	83	224	22	....	....	....
		11:48 a.m.	O_2	300	89	89	16	....	....	....

J. H. or W. W., but it diminishes the value of even a carefully standardized hyperventilation test as a tool for detecting individual differences.

C. Hyperventilation with Oxygen.—If the subject hyperventilates with oxygen instead of air, the 5 cycle count and the maximum delta index are both reduced. Table 2 shows a series of comparisons on 3 subjects. In only 2 out of 17 cases (H. D., 1/5/41, 2:02 p. m., and W. W., 2/8/41, 2:01 p. m.) did hyperventilation with oxygen produce a greater effect than a previous or subsequent hyperventilation at atmospheric oxygen tension. The difference is usually measurable and often definite (e.g., J. H., 12/4/40; H. D., 1/3/41, and W. W., 2/15/41). The counts and maximum delta indexes were often reduced to one fifth of their previous values by breathing oxygen. These measurements in controlled experiments fully confirm the impression of a "stabilizing" effect of oxygen gained from the summer's observations.

It may be noted (table 2) that the stabilizing effect of oxygen is still evident after the ingestion of sodium bicarbonate. After the ingestion of ammonium chloride the effects are more erratic. The only two tests in which the slow wave activity was greater when oxygen was breathed were both performed while the subject was in a state of metabolic acidosis (p_H 7.26 to 7.29).

The subjects consistently reported that when breathing oxygen they experienced less tingling sensation and less stiffness of facial muscles than usual. Such tingling as occurred appeared later in the test. (The beginning of and the degree of tingling or of sensations of dizziness, etc., were signaled at the time by the subject's raising his hand or pressing a push button on an extension cord that operated a signal pen writing on the electroencephalograph tape.) In 1 subject when breathing oxygen there was regularly a conspicuous absence of his usual peripheral vasoconstriction during and after hyperventilation.

D. Metabolic Acidosis and Alkalosis.—We originally believed that the electroencephalographic changes induced by hyperventilation depended directly on the changes in p_H or pCO_2 of the nerve tissue. The report by Gibbs, Lennox and Gibbs [2] that "in patients subject to petit mal seizures, carbon dioxide values tend to be abnormally low" and the statement by Nims and associates [11] that "the person with petit mal epilepsy responds to overventilation with a greater drop in the carbon dioxide content of the internal jugular blood . . . than does the nonepileptic control subject" are typical of the indirect evidence

11. Nims, L. F.; Gibbs, E. L.; Lennox, W. G.; Gibbs, F. A., and Williams, D.: Adjustment of Acid-Base Balance of Patients with Petit Mal Epilepsy to Overventilation, Arch. Neurol. & Psychiat. **43**:262 (Feb.) 1940.

on which this belief was based. We therefore anticipated that a metabolic acidosis induced by ingestion of ammonium chloride would favor and that an alkalosis induced by ingestion of sodium bicarbonate would hinder the appearance of slow waves during hyperventilation.

In six experiments the subjects ingested (in a single dose or in divided doses given over a period of two hours) 20 Gm. of sodium bicarbonate or 12 to 15 Gm. of ammonium chloride. (The subjects had no breakfast, and such doses taxed the tolerance of their digestive systems.) Satisfactory acidosis (p_H 7.27 to 7.29) was produced in 2 cases (table 2, H. D. and W. W.), but, to our surprise, it had no demonstrable effect one way or the other on the 5 cycle count or the maximum delta index during hyperventilation. The measured changes in p_H and pCO_2 of the serum after hyperventilation were as great as or even greater than in the control tests, but slow waves were produced in many cases with a p_H even below the initial p_H of the control tests. The pCO_2 fell to very low values (21 or 22 mm. of mercury), but the effect on the electroencephalogram was neither greater nor less than in the control tests.

The ingestion of sodium bicarbonate did not produce as great initial changes in the p_H or the pCO_2 as did that of ammonium chloride. The highest initial p_H produced was 7.49, and the additional changes (as measured at the end of hyperventilation) were rather erratic and the highest p_H (7.64) was no greater than the highest measured in 1 of the control tests. We are uncertain whether vasoconstriction tended systematically to mask greater changes that may have been produced or whether we were confronted by an effective homeostatic mechanism that stubbornly resisted our attempts to induce a greater alkalinity. We did attain a different combination of p_H and pCO_2 from that reached in the control tests in that the p_H was elevated to 7.59 (and higher) in the presence of a relatively high pCO_2 (27 to 29 mm. of mercury). It is clear from table 2, however, that such alkalosis as we produced neither favored nor hindered in any consistent way the development of slow waves in the electroencephalogram. Neither did the subjects experience any greater degree of tingling or stiffness of the muscles of face and hands or other indications of tetany. In short, the greatest metabolic acidosis or alkalosis that we could induce within two hours had far less effect on the results of hyperventilation than did changes in oxygen tension or changes in the blood sugar level.

E. Blood Sugar Level.—The most dramatic and consistent differences in the effects of standardized hyperventilation were induced by alterations in the blood sugar level. We confined our attention to the differences between the fasting state (the period of fasting ranging up to eighteen hours since the evening meal of the previous day) and

the hyperglycemia produced by a good luncheon or by ingestion of 35 cc. of Karo corn syrup (Red Label, diluted with 35 cc. of water and a little lemon juice). These situations represented the extreme situations encountered during our summer testing. The subjects' blood sugars, under these conditions, ranged from 74 to 160 mg. per hundred cubic centimeters, with one exceptionally low value of 57 mg. per hundred cubic centimeters. In figure 1 are presented graphically the results of several experiments on J. H. and H. D. in which significant changes in the blood sugar level were induced or took place spontaneously. In some of the experiments sodium bicarbonate or ammonium chloride was ingested during the day, and six or eight periods of hyperventilation were carried out (tables 1 and 2). The results shown in figure 1 are fairly typical, and the same stabilizing effect of a high blood sugar level has been demonstrated in many other subjects. Engel and Margolin [12] have also demonstrated in various clinical conditions of hypoglycemia the same dependence on the blood sugar level of the response to hyperventilation.

In all of the experiments illustrated in figure 1, with 1 exception, the spirometer was filled with air, either enriched with 800 cc. of oxygen or with the oxygen replenished. The curve for J. H. 12/4/40 O_2 falls far below the curve for J. H. 12/4/40 air. It should also be pointed out, however, that J. H. when breathing air did not invariably give such high 5 cycle counts. On another day (1/7/40) his 5 cycle count was only 16, with a blood sugar of 93 mg. per hundred cubic centimeters (table 2).

The relatively low points at the left of the lines (fig. 1) for H. D. 1/5/41 and 11/7/40 and for J. H. 12/4/40 and 11/12/40 are indications of the "first test effect" (cf. section B). In most of the experiments the first test (9:00 to 11:30 a. m.) gave the middle point in the curve. The point with the lowest blood sugar, at the left end of each curve, was obtained later (10:30 a. m. to 2:30 p. m.) and the high sugar point last, one-half hour after the ingestion of 35 cc. of Karo corn syrup. The first test in the morning tends to give a relatively high 5 cycle count. Apart from this, it should be noted that mere lapse of time, with constant blood sugar, does not alter the effect of hyperventilation (table 1, H. D., 11/7/40).

The maximum delta index can also be used as a measure of the change in the electroencephalogram, and a graph very similar to that in figure 1 could be based on the delta index, but the 5 cycle count reveals more delicately the early changes in the electroencephalogram. In fact, for most of our subjects the delta index usually does not increase significantly if the blood sugar is above 120 or 130 mg. per

12. Engel, G. L., and Margolin, S. G.: J. Nerv. & Ment. Dis. **93**:629, 1941.

hundred cubic centimeters, even though prominent delta episodes may appear on hyperventilation when the blood sugar is low.

F. Subjective Reports and Miscellaneous Observations.—It has already been noted (section C) that when the subjects breathed oxygen they reported less tingling and less stiffness of facial muscles than when the spirometer was filled with air. Increasing the blood sugar to a high level had a similar effect. Time and again the subjects reported a notable difference in the degree of tingling in the test after they had consumed the corn syrup, and two of them stated that the difference was like that on breathing oxygen. Often, as with oxygen, but not invariably, they reported complete absence of tingling, stiffness and dizziness.

Other subjective reports dealt with clearness of memory for incidents during the test. Sometimes instructions about breathing more or less deeply were correctly remembered; sometimes they were vaguely recalled by suggestion; sometimes completely forgotten. The subjects spoke of being "vague," "foggy," "partly out of contact," "lapsing in attention," "not knowing whether they followed the metronome or not." In many tests the experimenter spoke one or two numbers of two digits (such as "47" and, later, "63") during the last half minute of hyperventilation. By the end of the recovery period (two or three minutes) the subject often had forgotten the numbers, although he could recall clearly that they had been spoken, that he had repeated them to himself and had made an effort to remember them.

The occurrences of failure of memory, feelings of vagueness, etc., were by no means fortuitous. They did not occur when the blood sugar was high or when oxygen was breathed. They did occur quite regularly in those tests in which the 5 cycle count and the delta index rose to high values. The amnesia, confusion and vagueness were most definite when the delta index was highest. The partial clouding of consciousness associated with the appearance of large rhythmic delta waves has been pointed out before (Davis and Davis[13]). The particular item that we wish to emphasize here is the failure of memory. Events seemed to fade like a dream when one awakens. The appearance of delta waves does not imply unconsciousness, however. One subject correctly identified, by the rhythm of the sound of the pens of the electroencephalograph writers a few feet away, the recording of a large delta episode from his own brain. He reported after the test that there was "no subjective accompaniment" of the episode.

The spirograms show a characteristic modification when delta episodes appear. The breathing keeps accurate pace with the metronome,

13. Davis, H., and Davis, P. A.: A. Research Nerv. & Ment. Dis., Proc. (1938) **19**:50, 1939.

but full depth is not maintained. It is as if the automatic activity of regular deep breathing continued but the extra voluntary effort to make a maximal (or nearly maximal) inspiration was lacking. The subjects regularly responded correctly at such times to instructions to "breathe deeper," but they might or might not remember later that the instruction had been given. Figure 2 illustrates such an irregularity near the end of an otherwise very regular spirogram. Arrows indicate the time of appearance of clear delta episodes, such as are illustrated in figure 3, lower portion. In other tests with larger delta episodes the irregularities

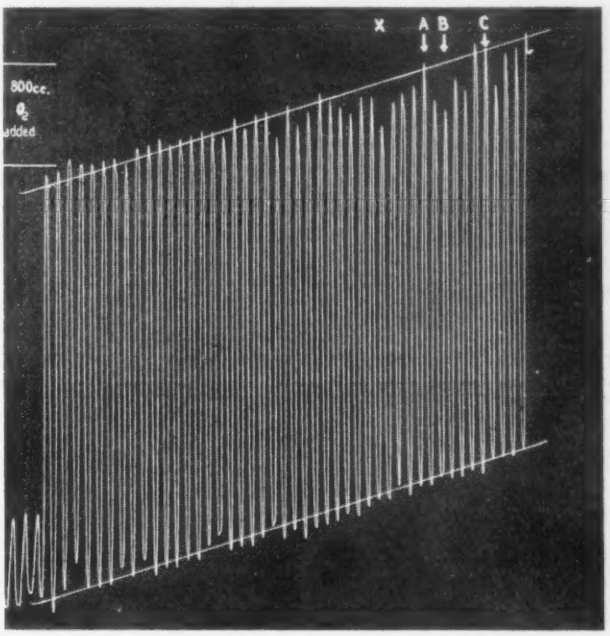

Fig. 2.—Spirogram of hyperventilation for H. D., 11/7/40, 2:34 p. m. The blood sugar measured 74 mg. per hundred cubic centimeters. The initial p_H was 7.415 and the final p_H 7.585. The initial pCO_2 was 27.5 and the final pCO_2 23.4. The 5 cycle count was 56; the maximum delta index, 14. The spirometer was filled with air plus 800 cc. of oxygen. The parallel guide lines (drawn subsequently) indicate "par" for this subject (20 cc. per breath per pound). Delta episodes appeared at arrows *A*, *B* and *C*. Figure 3 shows the electroencephalograms corresponding to *X* and to *C*.

were greater. It is noteworthy that the subjects did not identify subjectively, at the time or in retrospect, the 4 to 8 cycle activity (fig. 3, middle portion) which is the regular precursor of the typical delta episodes; neither did they betray signs associated with it in their breathing or other behavior.

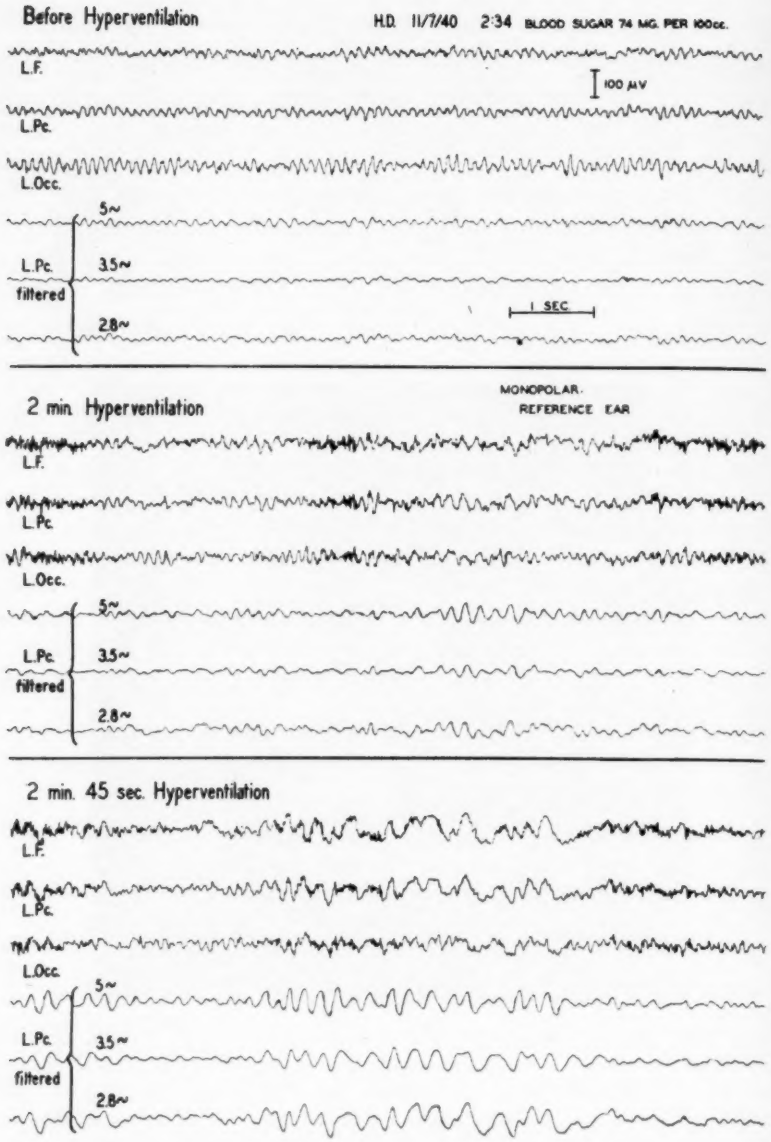

Fig. 3.—Electroencephalogram of H. D., 11/7/40; second test, 2:34 p. m. (see figure 2).

Top: control tracing before hyperventilation, showing 5 cycle count 0 and delta index 0.

Middle: tracing after two minutes of hyperventilation, showing increase in 5 cycle filtered record (fourth line) without significant increase in delta waves (fifth and sixth lines). The 5 cycle count for this ten second sample is 3; the delta index, 0. This sample corresponds to *X* in figure 2.

Bottom: tracing after two minutes and forty-five seconds of hyperventilation, showing the delta episode corresponding to *C* in figure 2. The 5 cycle count for this sample is 16; the delta index, 14.

COMMENT

Even when the gas mixture, pulmonary ventilation, serum p_H, pCO_2 and $[BHCO_3]$ and blood sugar are all standardized, there are still occasional variations from day to day in the reaction of a given subject. (Contrast in table 2, H. D., 1/5/41 with H. D., 3/8/41 and J. H., 12/4/40 with J. H., 1/7/41.) On each day the stabilizing effect of increasing the blood sugar, and also of increasing the oxygen tension, can be demonstrated, but evidently at least one other significant variable has still eluded us.

To some extent the unstabilizing effect of a moderately low blood sugar (75 to 90 mg. per hundred cubic centimeters) can be offset by increasing the oxygen tension (e.g., table 1, W. W., 3/8/41; table 2, W. W., 2/15/41, 9:18 and 9:55 a. m.), but further studies involving the use of insulin and of low tensions of oxygen are needed to determine the range of variation through which this mutual interaction takes place. It is already established (P. A. Davis [14]) that a small dose of insulin given in the fasting state will produce slow waves in the electroencephalogram *without hyperventilation* when, and for some time after, the blood sugar reaches its lowest level (53 to 75 mg. per hundred cubic centimeters). This condition is merely moderate hypoglycemia and is not to be confused with insulin coma. Also, low tensions of oxygen (60 to 75 mm. of mercury) produce similar changes *without hyperventilation* (Davis, Davis and Thompson [15]).

Gibbs, Williams and Gibbs [16] studied the effects of low oxygen, low carbon dioxide and low sugar content of the blood on the "cortical frequency spectrum," i.e., the electroencephalogram analyzed by means of the Grass analyzer. Reduction in each of the three components caused "a shift in energy toward the slow side of the spectrum," with an apparent increase in the total amount of energy except in case of the low blood sugar. This form of analysis and description is different from ours, but the facts are entirely consistent. Gibbs, Gibbs and Lennox [17] pointed out that a low blood sugar level increases the 3 per second wave and spike activity of petit mal epilepsy and that "if an abnormal formation is affected by variations in the level of sugar in the blood, it will respond to variations in the carbon dioxide of the blood."

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14. Davis, P. A.: J. Neurophysiol. **4**:92, 1941; Effect on Electroencephalogram of Changing the Blood Sugar Level, to be published.

15. Davis, P. A.; Davis, H., and Thompson, J. W.: Am. J. Physiol. **123**:51, 1938.

16. Gibbs, F. A.; Williams, D., and Gibbs, E. L.: J. Neurophysiol. **3**:49, 1940.

17. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Influence of Blood Sugar Level on Wave and Spike Formation in Petit Mal Epilepsy, Arch. Neurol. & Psychiat. **41**:1111 (June) 1939.

The interaction of dextrose and oxygen in maintaining a normal pattern of nervous activity is not surprising, as the dextrose must be oxidized to support metabolism and dextrose is generally conceded to be the fuel of choice in nerve tissue. The compensation by excess of one component for a partial deficiency of the other suggests the operation of the familiar mass law, but the resemblance may be purely formal and the actual mechanisms are certainly complex (Gerard [18]). Other evidence of the compensatory relation between dextrose and oxygen in the nervous system appears elsewhere, for example, in the work of McFarland and Forbes [19] (cf. also Gellhorn, Ingraham and Moldavsky [20]) on visual acuity. Empirically, the value of high blood sugar in offsetting a reduced oxygen supply is recognized in aviation medicine in the advice to aviators embarking on a long mission at high altitude that they eat well before starting and partake of food (chocolate, etc.) during the flight (von Diringshofen [21]).

The effect of hyperventilation on the electroencephalogram seems to be similar to that produced by lack of sugar or oxygen or both, i.e., by cerebral anemia. Indeed, the simplest single explanation of our results is the assumption that the hyperventilation, presumably by producing a change in p_H or pCO_2, induces cerebral vasoconstriction and partial anemia of the brain. Lennox, Gibbs and Gibbs [22] demonstrated a reduction in cerebral blood flow as a result of hyperventilation and interpreted the reaction as directed toward maintaining a relatively constant carbon dioxide tension of the brain (see also Lennox and Gibbs;[23] Gibbs, Gibbs and Lennox [24]). We have called attention to the evidences of *peripheral* vasoconstriction in one of our subjects, particularly in those tests showing the greatest electroencephalographic changes. Whether the increased oxygen and blood sugar act to prevent the cerebral vasoconstriction, as they seem to counteract the peripheral vasoconstriction, or whether they enable the brain to obtain sufficient oxygen and dextrose from a reduced supply of blood is uncertain.

The failure of metabolic acidosis or alkalosis to affect the reaction to hyperventilation indicates that if the stimulus for vasoconstriction

18. Gerard, R. W.: Anoxia and Neural Metabolism, Arch. Neurol. & Psychiat. **40**:985 (Nov.) 1938.

19. McFarland, R. A., and Forbes, W. H.: J. Gen. Physiol. **24**:69, 1940.

20. Gellhorn, E.; Ingraham, R. C., and Moldavsky, L.: J. Neurophysiol. **1**:301, 1938.

21. von Diringshofen, H.: Medical Guide for Flying Personnel, Toronto, University of Toronto Press, 1940.

22. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: J. Neurol. & Psychiat. **1**:211, 1938.

23. Lennox, W. G., and Gibbs, E. L.: J. Clin. Investigation **11**:1155, 1932.

24. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Am. J. Physiol. **111**:557, 1935.

is the p_H or the pCO_2 it is the sudden change in these values, and not their absolute level, that is effective. Contrary to the hypothesis that it is the change in p_H of the nerve tissue that produces the slow electrical waves of hyperventilation is the tendency of alkalinity of nerve tissue to produce excitation and overactivity (Dusser de Barenne, McCulloch and Nims [25]). The picture seen in hyperventilation is one of depressed function, fully consistent with partial cerebral anemia.

Another minor item favoring the vascular hypothesis is the occasional appearance of "relapses" or delayed reappearance of slow waves and delta episodes a minute or more after the end of hyperventilation. In our experiments the record usually returned nearly to normal within half a minute, or at most a minute, after the end of hyperventilation. We observed clearly in 2 cases that the "relapse" was associated with apnea, pallor and beginning cyanosis and that the slow waves disappeared when the subject was instructed to take two deep breaths. The relapse could not have been due to a recurrence of general alkalosis, for carbon dioxide was accumulating in the tissues and blood stream during the period of apnea, but it could have been the result of general or local anoxia. "Relapses" occurred most frequently with the subject who had the greatest peripheral vasoconstriction, and it is interesting that in one experiment he had a "relapse" after each of three tests in which he breathed air and none after the three tests in which he breathed oxygen.

Our hypothesis that the slow wave reaction depends on local deficiency of oxygen or blood sugar differs slightly from the interpretation implicitly offered by Nims and associates [11] for the precipitation of petit mal lapses by hyperventilation. These investigators analyzed blood collected from the internal jugular vein during and after hyperventilation and found that patients suffering from petit mal epilepsy, unlike their normal controls, showed an "acid-base loop" that suggests the appearance of fixed acid in the brain tissue, i. e., a metabolic acidosis. They expressed the belief that "the mechanisms which regulate the physicochemical state of the fluids of the brain are somewhat impaired in petit mal epilepsy, so that the person with such a condition is not able adequately to control or quickly adjust the acid-base balance when it is disturbed by overventilation." They also pointed out that the rate of blood flow in the cerebral capillaries is one of several factors contributing to this regulation, but it is not clear from their observations or from our own whether the precipitation of petit mal lapses depends on an overactive vascular reaction or on an abnormal sensitivity of the brain to anoxia and hypoglycemia or to a disturbance of its acid-base balance.

25. Dusser de Barenne, J. G.; McCulloch, W. S., and Nims, L. F.: J. Cell. & Comp. Physiol. **10**:277, 1937.

And it must be recalled that the relation of the wave and spike of petit mal to the normal rhythmic delta waves is still uncertain.

We do not deny the value of hyperventilation as a diagnostic test if it causes the appearance of the wave and spike formation, but it is dangerous to interpret large rhythmic delta waves, even if they arise before the third minute, as indicating "instability" or abnormality of the nervous system. First of all the hyperventilation must be standardized. Some men can breathe half as much again as our arbitrary standard, while other subjects cannot (or will not) breathe more than half, or even a third, the required amount. Also, a standard (preferably fairly high) blood sugar level must be assured by performing the test only after a meal or by giving available carbohydrate as a routine preparation. But mere standardization is not sufficient. The test must then be evaluated empirically on a large series of normal and abnormal subjects to determine its diagnostic significance. Unfortunately, the standardization is elaborate and requires intelligent cooperation of the subject. Such standardization will rob the test of the simplicity that has made it so attractive an addition to routine electroencephalographic examinations.

SUMMARY

Electroencephalograms were recorded on normal male subjects during and after three minute periods of standardized hyperventilation. Breathing was timed by metronome at 15 breaths per minute and the depth adjusted by instructing the subject according to the excursion of the drum of a Roth-Benedict metabolism apparatus to 20 cc. per pound (44 cc. per kilogram) of body weight.

Blood from a finger pad, taken just before and just after hyperventilation, was analyzed for total carbon dioxide, p_H (serum) and sugar. In spite of variations in the postventilation values caused by peripheral vasoconstriction, it is inferred that the standardization of breathing produces a considerable and fairly constant respiratory alkalosis (p_H increased by 0.20 unit; carbon dioxide tension reduced by 18 mm. of mercury).

As a measure of the modification of the electroencephalogram, we counted the number of waves above an arbitrary size, never reached in normal control records, that passed an electrical filter broadly tuned to 5 cycles. We also measured a modified "delta index." Repeated tests on a given subject at intervals of fifteen minutes to three and a half hours produced fairly constant increases in the 5 cycle count and the maximum delta index (table 1).

Metabolic alkalosis (p_H up to 7.64 before hyperventilation) and acidosis (p_H down to 7.29) produced by oral ingestion of sodium

bicarbonate and ammonium chloride respectively caused no significant change in the effect of hyperventilation on the electroencephalogram (table 1).

Hyperventilation with oxygen produced less alteration in the electroencephalogram than when air maintained at 20 per cent oxygen content was breathed (table 2).

Low blood sugar (80 mg. per hundred cubic centimeters or less) favored the appearance of delta waves, and a high sugar level (over approximately 120 mg. per hundred cubic centimeters) strongly tended to prevent their appearance. At a given blood sugar level there were considerable individual differences in the amount of 5 cycle and delta activity, and the subjects varied somewhat in their responses from day to day, but the effect of low blood sugar is so important that the level must be controlled if hyperventilation is to be standardized as a test for stability of the electroencephalogram.

The subjects reported less tingling sensation and stiffness of facial muscles and showed less peripheral vasoconstriction when breathing oxygen or when the blood sugar level was high than under the opposite circumstances.

When large clear trains of delta waves appeared the subjects often reported lapses of attention or loss of precise memory for events during the test. Their spirograms showed that full standard depth of respiration was not maintained at such times (fig. 2).

In interpretation, it is suggested that hyperventilation causes the appearance of 5 cycle and delta waves by inducing cerebral vasoconstriction, which in turn causes diminution in the supply of oxygen and dextrose to the cerebral cortex.

DISCUSSION

DR. FREDERIC A. GIBBS, Boston: These exceedingly interesting observations should certainly be taken into account by those who use overventilation as a clinical test. I think that my associates and I can agree with the authors except for their conclusion that the slow waves which appear with overventilation are the result of low oxygen content. Our measurement of gases in the blood entering and leaving the brain has convinced us that it is the subjects who *do not* have good cerebral vasoconstriction who show slow waves with overventilation. A constrictor response of the cerebral blood vessels when the arterial carbon dioxide drops helps to maintain the cerebral carbon dioxide tension at or near the preoverventilation level. This is in effect a homeostatic mechanism for cerebral carbon dioxide regulation. It is definitely advantageous and is found to be severely disorganized in petit mal epilepsy. The drop in oxygen which accompanies the constriction associated with overventilation is insufficient to slow the electrical activity of the cortex. Our data indicate that it is the subject whose carbon dioxide drops and whose cerebral oxygen content stays up who shows the slow waves. The subject who has sufficiently strong vasoconstriction to lower greatly his oxygen supply is a superman who will be able to overventilate for a long time without showing the

slowing in cerebral activity which has been referred to. Vasoconstriction so extreme that it causes a drop in oxygen sufficient to produce slowing of cortical activity does not occur with overventilation because as this point is approached the dilator effect of a low oxygen content appears and the constriction to low carbon dioxide tension is abandoned. It is known that if a subject is made to overventilate in an atmosphere which is low in oxygen he is at a great disadvantage, for his carbon dioxide tension level determines how much leeway he has for constriction. We should explain the response observations reported here by saying that by raising the arterial oxygen content and the arterial sugar level above normal the authors have given an advantage to the homeostatic mechanism for cerebral carbon dioxide regulation, for under these conditions vasoconstriction can proceed further than would otherwise be possible without reducing vital nutrient supplies to a dangerously low level.

Dr. Robert S. Schwab, Boston: This is obviously a controversial question, and I am not entering into any discussion of Dr. Gibbs's remarks. My associates and I at the Massachusetts General Hospital have worked with the same problem of the relation of overventilation and the blood sugar level. It appears from the work of Dr. Davis that the blood sugar level is a critical and important fact to determine in any case in which an electroencephalogram is being taken. It would seem desirable to make half-hourly blood sugar determinations on a large number of normal and abnormal subjects to see whether in the ordinary course of the day there occur spontaneously any of these critical alterations in the blood sugar level. Perhaps this type of hypoglycemia can be associated with irritability or certain behavior disorders.

I should point out that merely giving sugar to a subject does not insure the elevation of his blood sugar in a half-hour or an hour. We know that under emotional stress absorption from the gastrointestinal tract is greatly prolonged. One patient in our series to whom we gave 200 Gm. of dextrose showed an increase in the blood sugar in an hour of only 10 mg., from 70 to 80 mg., due to nervous tension.

We found in our work that there was little difference in overbreathing if 10 per cent oxygen, room air or 90 per cent oxygen was inspired. There was a little protection against the slow delta waves if air with a high oxygen content was inspired, but it was insignificant. We found that the blood sugar level was critical, as the authors have mentioned. We also noted in our series of cases that when delta waves with low blood sugar levels developed from overbreathing the patients become sluggish in their responses and had prolonged reaction times to visual stimulation.

My final point is an attempt to corroborate the authors' thesis that vasoconstriction appears to be an important cause of these delta waves. If that is so, it would seem logical that a vasodilator would eliminate them. In 2 patients who could produce delta waves by overbreathing the effect of the inhalation of amyl nitrite, a vasodilator, was observed on the occurrence of these waves. During the third minute of overbreathing there was an abundance of delta waves, about 43 per cent of the entire record. The technician then gave the patient some amyl nitrite on a cloth and asked him to breathe through his mouth. Very rapid vasodilation occurred, and the delta waves disappeared during this part of the record, there being only 4 per cent of delta waves. The amyl nitrite was kept before the patient's mouth for thirty seconds and then withdrawn. Twenty seconds later, the patient continuing to overbreathe all of the time, the delta waves came back in increased numbers, constituting 62 per cent of the record. Both patients were

unaware of the use of amyl nitrite because they were breathing through their mouths and did not smell it and it was not kept up long enough to produce any syncopal effect. These observations suggest that Dr. Davis' idea that delta waves are due to vasoconstriction is a sound one.

DR. JOHN KERSHMAN, Montreal, Canada: I would ask one question. Does the administration of dextrose or the maintenance of a high blood sugar prevent the appearance of delta waves in epileptic patients?

DR. H. DAVIS, Boston: We have obviously many pieces in the picture puzzle that must be pieced together. I am much obliged to Dr. Gibbs for the additional information he has put before you, which is certainly part of the whole story and will have to be incorporated sooner or later into any interpretation; I thank also Dr. Schwab for his observations and the striking demonstration of the effect of amyl nitrite in abolishing delta waves.

As to the blood sugar in epileptic patients, I have no cases of my own, but I just asked Dr. Schwab if he could give me any information. He pointed out that in 1 of the cases he just presented the subject was epileptic and that the blood sugar at the time of the test was 160 mg. per hundred cubic centimeters. In other words, it was not possible to stabilize that particular epileptic patient by elevating the blood sugar even to a very high level. There certainly are individual differences in the susceptibility to a given amount of overventilation, and I do not wish to imply for a moment that the test is not useful in revealing exactly those individual differences. My point is simply that one must control some of the other factors in order to draw sound and clear conclusions.

VASCULAR AND INTERSTITIAL CELL CHANGES IN THIAMINE-DEFICIENT ANIMALS

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BOSTON

Prickett [1] seems to have been the first to describe hemorrhages in the brains of thiamine-deficient rats. These lesions were usually recent, small and bilaterally located in the vestibular nuclei, the nucleus solitarius, the abducens nucleus, the cerebellar nuclei and the cerebellum. In several animals which had been restored clinically from deficiency and subsequently made thiamine deficient again, the hemorrhages were old and were accompanied by proliferation of the interstitial and vascular connective tissues or replaced by scars. Degeneration of myelin sheaths was not seen in Marchi or Busch preparations, but in Nissl preparations chromatolysis and sclerosis of cell bodies were observed in the vestibular and cerebellar nuclei. Similar lesions were also noted by Church [2] in thiamine-deficient rats.

Prickett [1] observed the same type of hemorrhage in thiamine-deficient pigeons. As in the rat, the lesions were located chiefly in the vestibular and cerebellar nuclei, but also in the optic lobes and the cerebral hemispheres. Cellular changes were seen in the same areas. Other investigators [3] have also observed hemorrhagic lesions in thiamine-deficient pigeons.

The significance of these lesions has not been satisfactorily explained. Prickett expressed the belief that the hemorrhages were of no importance

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1. Prickett, C. O.: The Effect of a Deficiency of vitamin B_1 upon the Central and Peripheral Nervous Systems of the Rat, Am. J. Physiol. **107**:459, 1934.

2. Church, C. F.: Functional Studies of the Nervous System in Experimental Beriberi, Am. J. Physiol. **111**:660, 1935.

3. (*a*) Alexander, L.; Pijoan, M.; Myerson, A., and Keane, H. N.: Beriberi and Scurvy: An Experimental Study, Tr. Am. Neurol. A. **64**:135, 1938. (*b*) Zimmerman, H. M.: The Pathology of the Nervous System in Vitamin Deficiency, Yale J. Biol. & Med. **12**:21, 1939. (*c*) Alexander, L.: Wernicke's Disease: Identity of Lesions Produced Experimentally by B_1 Avitaminosis in Pigeons with Hemorrhagic Polioencephalitis Occurring in Chronic Alcoholism in Man, Am. J. Path. **16**:61, 1940.

with respect to the symptoms, since the symptoms could be so readily abolished by vitamin B_1 administration. For the same reason, Church suggested that the hemorrhages were secondary to metabolic changes in the vestibular nuclei. Several workers [4] have commented on the topographic and histologic similarity of the hemorrhages in thiamine-deficient pigeons to lesions which occur in patients with Wernicke's syndrome. Alexander [3c] went even further and stated that the etiologic factor in the two conditions is identical, namely, vitamin B_1 deficiency, and to this vitamin he attributed antiangiodegenerative powers.

From studies of human postmortem materials other investigators [5] have also suggested that Wernicke's diesase may be due to a deficiency of thiamine, as hemorrhagic and degenerative lesions, most marked near the third and fourth ventricles, are to be observed in patients with vitamin B_1 deficiency and in others suffering from conditions commonly associated with this deficiency, i. e., chronic alcoholism, carcinoma of the gastrointestinal tract and vomiting of pregnancy.

The clinical manifestations of thiamine deficiency in pigeons and the methods by which these symptoms are produced [6] and the accompanying neuronal lesions [7] have already been described in detail. In this paper the nature and topographic distribution of the hemorrhages, the mechanism of their production and the associated changes in the interstitial tissues will be considered.

DIETARY METHODS AND TYPES OF ANIMALS

By utilizing principles of dietary management [7] and methods [6] described in detail before, very acute, moderately acute and chronic deficiency in thiamine were induced in pigeons. For clarity these methods will be described briefly. Those pigeons which were to become acutely deficient were placed for three weeks on a preliminary dietary regimen consisting of feeding 20 Gm. of diet III (alcohol-extracted casein, 20 per cent; cod liver oil, 4 per cent; peanut oil, 4 per cent; salt mixture, 2 per cent; corn starch, 60 per cent; autoclaved yeast, 10 per cent, and a vitamin K concentrate) by tube and injecting 50 micrograms of thiamine hydrochloride intramuscularly each day. This treatment accustomed the birds to

4. Zimmerman.[3b] Alexander.[3c]

5. Campbell, A. C. P., and Biggart, J. H.: Wernicke's Encephalopathy (Polioencephalitis Hemorrhagica Superior): Its Alcoholic and Non-Alcoholic Incidence, J. Path. & Bact. **48**:245, 1939. Ecker, A. D., and Woltman, H. W.: Is Nutritional Deficiency the Basis of Wernicke's Disease? Report of a Case, J. A. M. A. **112**: 1794 (May 6) 1939.

6. Swank, R. L., and Bessey, O. A.: Avian Thiamin Deficiency: Characteristic Symptoms and Their Pathogenesis, J. Nutrition **22**:77, 1941.

7. (*a*) Swank, R. L.: Avian Thiamin Deficiency: A Correlation of the Pathology and Clinical Behavior, J. Exper. Med. **71**:683, 1940. (*b*) Swank, R. L., and Prados, M.: Avian Thiamine Deficiency: II. Pathologic Changes in the Brain and Cranial Nerves (Especially the Vestibular) and Their Relationship to the Clinical Behavior, Arch. Neurol. & Psychiat. **47**:97 (Jan.) 1942.

tube feeding and facilitated the neuronal studies described elsewhere.[7b] Twenty of the birds were then made very acutely deficient in thiamine by discontinuing the thiamine chloride and changing to diet II (diet III minus the autoclaved yeast), which was also fed in 20 Gm. amounts daily. Opisthotonos developed in seven to ten days and the birds were killed or were restored to normal by administration of thiamine hydrochloride as soon as this symptom was recognized. Twelve birds were made less acutely deficient, or moderately acutely deficient in thiamine by discontinuing thiamine hydrochloride and reducing the amount of the food intake. Opisthotonos developed in ten to fourteen days, and the birds were killed or were given thiamine hydrochloride for the purpose of restoring them to normal as soon as this symptom appeared. Ten birds were made chronically deficient in thiamine by feeding them 20 Gm. of diet III and 15 to 20 micrograms of thiamine hydrochloride daily (60 to 80 per cent of the normal requirement). As a consequence of this partially thiamine-free ration, they were depleted of thiamine slowly, and accordingly ataxia, either of the "cerebellar" or of the "locomotor" type,[7b] developed, without opisthotonos.

Twelve other pigeons received less than the normal caloric intake of diet III (10 Gm. daily) and no thiamine hydrochloride and were allowed to become severely deficient in thiamine. Opisthotonos developed in fourteen to twenty-five days and was exhibited for twenty-four to seventy-two hours before the birds were killed. The depletion of thiamine in the brains of these birds was both much slower and more complete than in the acutely deficient pigeons and was more complete than in any of the chronically deficient birds. They will be referred to as having severely acute thiamine deficiency.

In addition, 13 kittens and cats were made thiamine deficient. They were fed diet III by tube and were made acutely or chronically deficient, as was done in case of pigeons, by varying the amount of the food and the thiamine intake. In seven to ten days the kittens with very acute deficiency became ataxic, then prostrate, and soon after died. Kittens with less acute deficiency, which received a diet supplemented with thiamine hydrochloride, manifested the same symptoms in ten to twenty days. In all of these animals the deficiency was severe as well as acute in onset.

HISTOLOGIC TECHNICS

The brains of the acutely and many of the chronically deficient pigeons were stained in blocks by the silver nitrate method of Ramón y Cajal, as described in detail elsewhere.[7b] The brains of other pigeons with chronic deficiency and of the pigeons with severely acute deficiency were fixed in solution of formaldehyde U. S. P., embedded in paraffin, sectioned serially and stained by the methods of Nissl and Van Gieson and by the silver carbonate method for connective tissue. In a number of instances the latter method was modified so that it stained both the connective-vascular tissues and the neurons. The technic was as follows: Formaldehyde-fixed, paraffin or frozen sections were placed in a solution of 2 per cent silver nitrate plus 15 drops of pyridine for each 50 cc. of solution for twenty-four hours. They were washed rapidly and placed in a 5 per cent solution of silver carbonate plus 40 drops of pyridine for each 50 cc. of solution and heated to 60 degrees for one hour (until dark brown), and rapidly washed again. The sections were reduced in a 2 per cent concentration of solution of formaldehyde U. S. P., toned in a solution of gold chloride as usual until they appeared slightly purple, fixed in sodium thiosulfate and mounted in xylene balsam.

After the kittens were killed their brains were placed in a mixture of solution of formaldehyde U. S. P. and ammonium bromide or in dilute solution of for-

maldehyde U. S. P. (1:10). Tissues from the cerebral cortex, the thalamus, the midbrain, the pons and the medulla oblongata which had been fixed in the solution of formaldehyde and ammonium bromide were sectioned while frozen and stained for oligodendroglia by the silver carbonate method of del Río Hortega and for astrocytes by the Cajal gold chloride–mercury bichloride method. Formaldehyde-fixed tissues were also sectioned while frozen and stained for connective and vascular tissue by the Hortega silver carbonate method for connective tissue. Tissues were also embedded and sectioned in paraffin and stained by the method of Nissl and the modification of the silver carbonate method for connective tissue and neurons already described.

RESULTS

Studies on Pigeons.—A. Hemorrhages: Hemorrhagic lesions in our thiamine-deficient pigeons developed in three stages. 1. Hyperemia, the first of these, was present alone for a variable time (fig. 1 *A*), perhaps a few hours to several days. 2. Next, the perivascular (Virchow-Robin) spaces of the arterioles, venules and capillaries became distended, first with fluid and then with red blood cells (fig. 1 *B*), the endothelial lining of the blood vessels remaining intact. 3. Finally, the red blood cells infiltrated the surrounding tissues (fig. 3). In many cases the vascular changes never progressed further than the stage of hyperemia, but hyperemia always accompanied perivascular and infiltrating hemorrhages, except in curative experiments. It is no doubt important that white blood cells were rarely seen with the red blood cells in either type of hemorrhage.

Pigeons with very acute deficiency: In these pigeons hemorrhages were confined to nuclei near the fourth ventricle which receive vestibular nerve fibers (zone 1, fig. 2 *C*). Hyperemia was present throughout this region and in the cerebellum. The hemorrhages were very small, perivascular and not numerous. They were observed in all cases either in the nucleus magnocellularis or in the medial part of the cerebellar nuclei and occasionally in Deiters' nucleus and the dorsal part of the reticular formation.

Pigeons with moderately acute deficiency: In these pigeons the vascular lesions were more widespread. Hyperemia was found throughout the vestibular region (zone 1 and 2, fig. 2 *C*) and the cerebellum in all cases and was observed in the lateral part of the thalamus (nucleus rotundus and the lateral nucleus of the thalamus), the nucleus isthmi and other nuclei of the optic lobes (zone 3, fig. 2 *A* and *B*) in a few cases. Hemorrhages were much more numerous and slightly larger than were observed in the more acutely deficient pigeons and were scattered throughout the areas which exhibited hyperemia. The hemorrhages were chiefly perivascular, but in the nucleus magnocellularis (fig. 4 *A*) in 2 cases and in the nucleus rotundus of the thalamus (fig. 4 *B*) in 1 case red blood cells had infiltrated the surrounding tissues.

As in the pigeons with very acute deficiency, hemorrhages were never consistently present in any one nuclear mass. The nucleus magnocellularis and the cerebellar nuclei were involved most frequently and the remaining nuclei in zones 1, 2 and 3 occasionally. Although

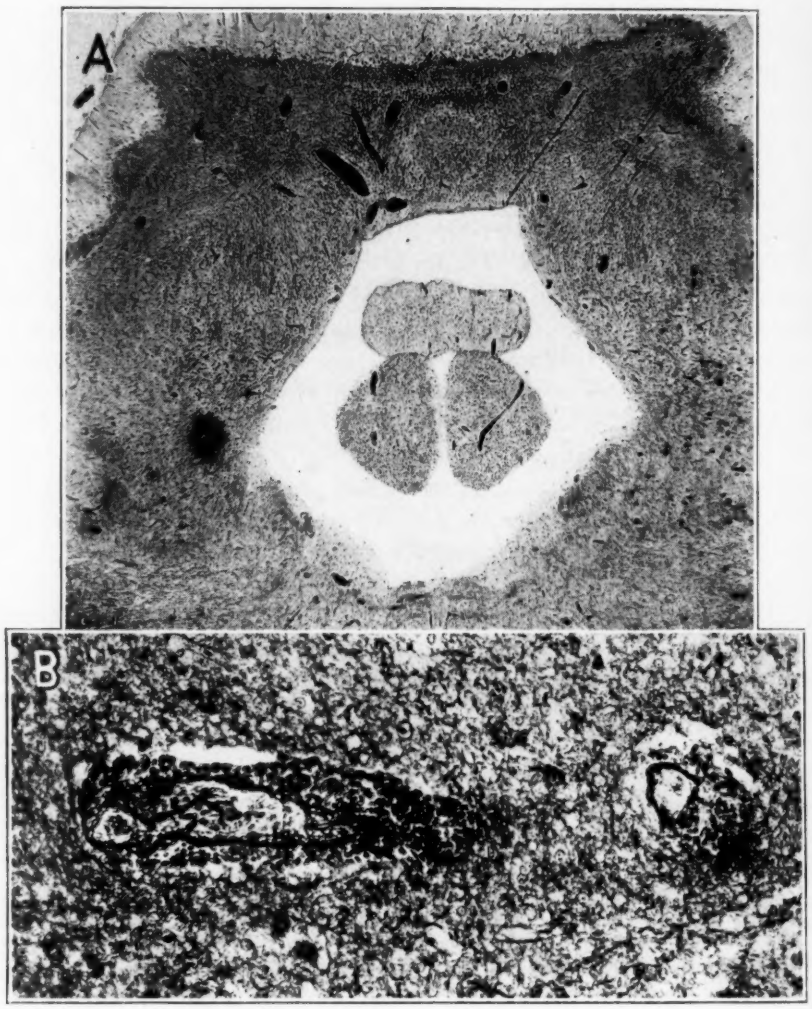

Fig. 1.—*A*, lower part of the pons, showing marked hyperemia. Note infiltrating hemorrhage to the left of the fourth ventricle. Silver connective tissue method; × 20. *B*, region of the nucleus magnocellularis in the medulla oblongata, showing perivascular hemorrhages. The perivascular space to the right is distended with fluid and a few red blood cells. Silver connective tissue method; × 300.

hyperemia was present in the cerebellum in all cases, small hemorrhages were seen there in only 1 case.

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Pigeons with severely acute deficiency: A marked change in the character of the vascular lesions was to be seen in the brains of pigeons with severely acute deficiency. Hyperemia was present in the entire brain, although most marked in zones 1, 2 and 3 (fig. 2). Most of

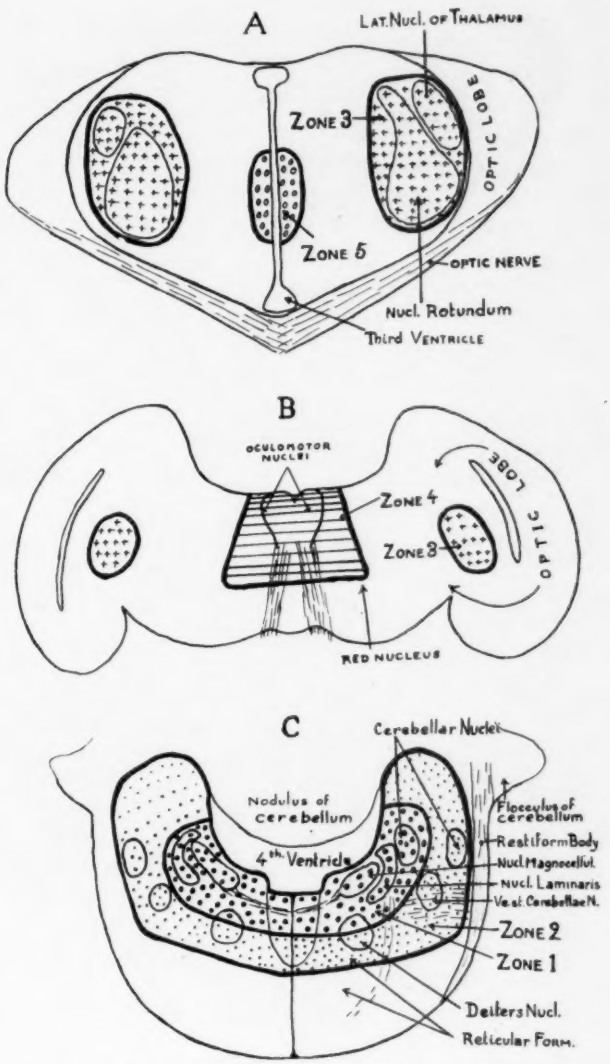

Fig. 2.—Schematic illustrations to show the distribution of hemorrhages in pigeons with the different types of deficiency. *A* is a section of the thalamus; *B*, of the midbrain, and *C*, at the level of the fourth ventricle. Zone *1* is indicated by heavy dots; zone *2*, by small dots; zone *3*, by crosses; zone *4*, by horizontal lines, and zone *5*, by circles.

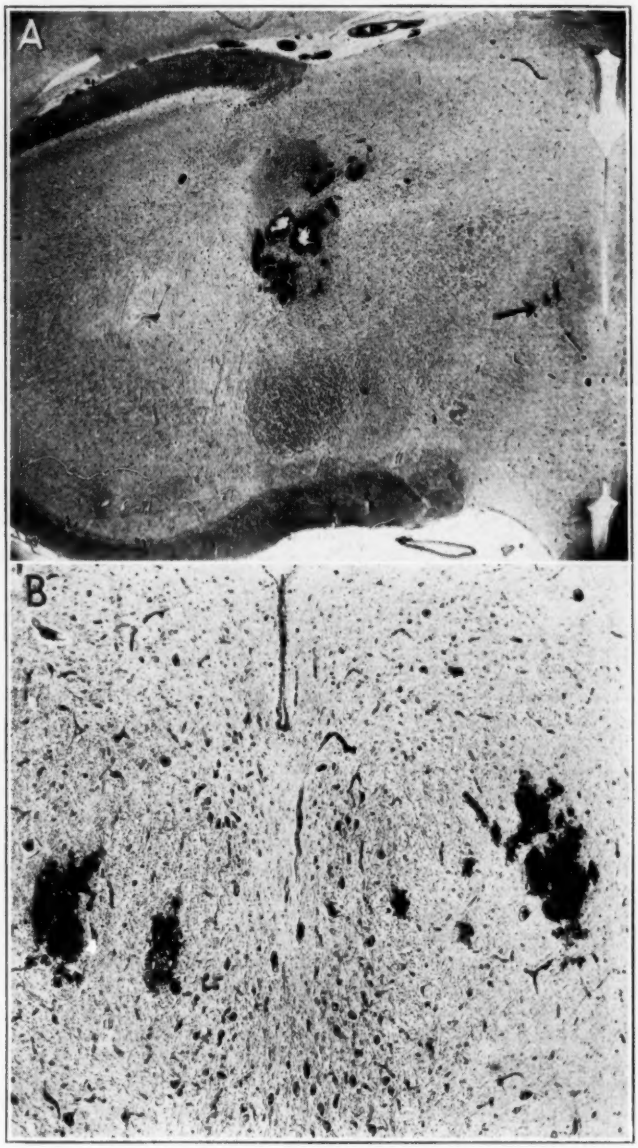

Fig. 3.—*A*, photomicrograph of the thalamus, showing large infiltrating hemorrhages with central necrosis in the nucleus rotundus and the lateral nucleus of the thalamus and small perivascular hemorrhages (arrow) in the paramedian region of the third ventricle. Silver connective tissue; × 13.

B, bilateral infiltrating hemorrhages in the vicinity of the nuclei of the oculomotor nerve. Silver connective tissue; × 27.

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the perivascular hemorrhages were much larger and greatly distended the Virchow-Robin spaces, and many large infiltrating hemorrhages were to be seen. Zones 1, 2 and 3 contained many more both large

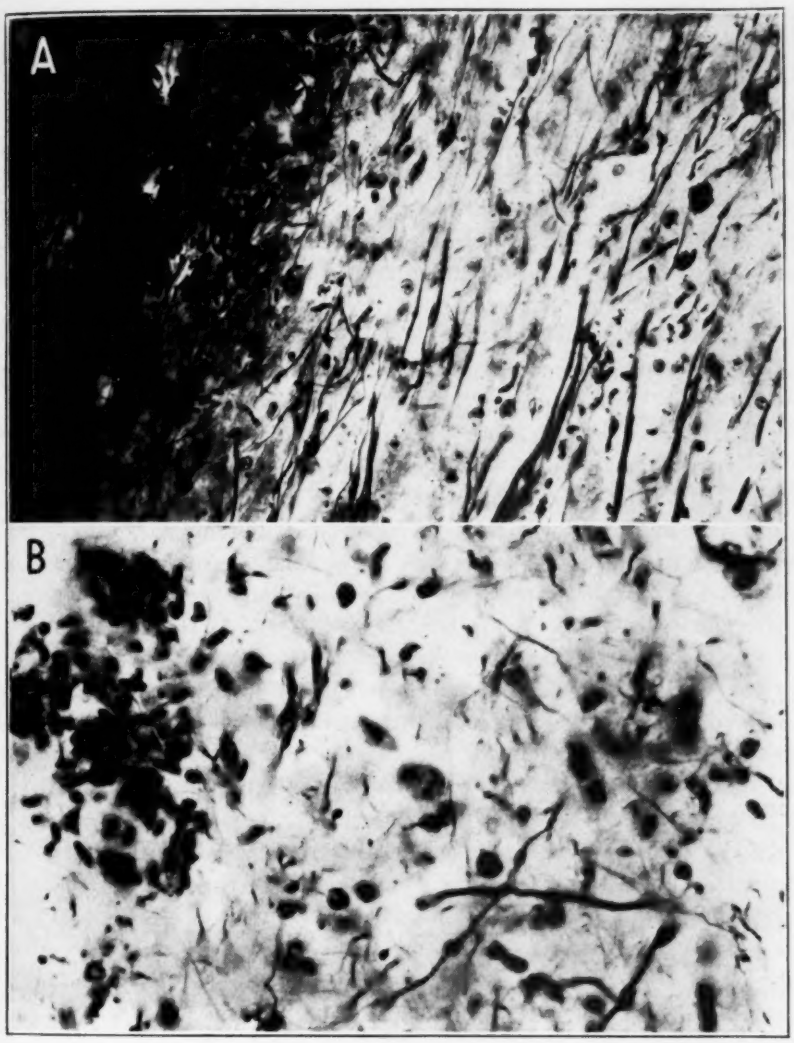

Fig. 4.—*A*, infiltrating hemorrhage in the nucleus magnocellularis. Note hemorrhage to the left and numerous degenerating axons to the right. Cajal block silver method; × 458.

B, infiltrating hemorrhage in the nucleus rotundus of the thalamus. Note hemorrhage to the left and degenerating nerve fibers surrounding it. Cajal block silver method; × 635.

and small hemorrhages than were hitherto observed. In 3 pigeons very small perivascular hemorrhages were seen in the oculomotor nucleus (fig. 3 *B*) and the surrounding reticular region (zone 4, fig. 2 *B*), and in 2 others a single bilateral perivascular hemorrhage was seen in the region of the third ventricle (zone 5, fig. 3 *A*). By far the largest infiltrating hemorrhages were observed in the lateral part of the thalamus in the nucleus rotundus (fig. 3 *A*), and in 2 cases these were visible grossly in stained sections and produced central necrosis. It was not unusual for small blood vessels to become dilated on entering a region containing hemorrhages. Red blood cells were seen in the ventricles in almost all of the pigeons with severely acute deficiency. Although this may have been due to trauma in 1 or 2 instances, as study of control and other materials indicated, there can be no doubt that trauma was not a factor in most of these cases.

Pigeons with chronic deficiency: The brains of all the chronically deficient pigeons exhibited generalized hyperemia. In 1 animal only hemorrhages were seen, and this in the nucleus magnocellularis.

B. Relation of Vascular to Neuronal Lesions: In another study[7b] the neuronal changes in the brain and cranial nerves of thiamine-deficient pigeons were described in detail. Many of the pigeons included in that study were also employed here. In the very acutely deficient birds early histologic changes were seen in most cases in the central terminations of the vestibular nerves to the nucleus magnocellularis and less frequently in terminations to the cerebellar nuclei and to Deiters' nucleus. Cell bodies in the nucleus magnocellularis frequently were shrunken but elsewhere were normal. Many basket axons in the cerebellum also exhibited early changes. In moderately acutely deficient animals more advanced changes were present in the nucleus magnocellularis. Likewise, the changes in Deiters' nucleus, the cerebellar and vestibulocerebellar nuclei and the reticular formation had increased. In several of these birds degenerative cellular as well as axonal changes were seen in the nucleus rotundus of the thalamus and in the optic lobes. In most pigeons with moderately acute deficiency changes in the cell bodies were seen in the nucleus magnocellularis and the reticular formation, and many moss and basket fibers in the cerebellum were degenerated. In chronically deficient pigeons, in addition to the alterations already described, changes in the cells and axons of the oculomotor and trochlear nuclei and in axons of the hypothalamus were to be seen. Degeneration in the cerebellum was essentially the same as that observed in the acutely deficient birds. In chronically deficient pigeons the cellular changes were less severe and axonal changes more severe than in acutely deficient pigeons.

The distribution of the vascular changes, as described in the preceding section of this paper, was the same as that of the neuronal changes just

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described. In very acutely deficient pigeons degeneration of neurons and vascular lesions were confined to zone 1, figure 2 *C*, and to the cerebellum. In pigeons with moderately acute deficiency zones 1 and 2, and occasionally zone 3, contained both degenerating neurons and vascular lesions. In the birds with severely acute deficiency hyperemia was generalized, but hemorrhages appeared only in the zones where neuronal degeneration was detectable, namely, zones 1, 2 and 3 and occasionally 4 and 5 (fig. 2).

Hemorrhages were almost always surrounded by degenerating axons or cells, the severity of one frequently, but not always, being a reflection of the severity of the other (fig. 4). It was not unusual, however, to find degenerating neurons unaccompanied by vascular lesions. It seems apparent from this and other observations that the parenchymal changes preceded the vascular lesions.

C. Changes in the Blood Vessels: These were noted chiefly in the adventitia and the perivascular regions of the arterioles, venules and capillaries. No abnormality of the intima was noted in any of our animals. The early changes (those accompanying hyperemia and early perivascular hemorrhages) consisted of thickening and increase in the number of adventitial connective tissue fibers, chiefly the reticulum. This alteration occurred soon after appearance of the neuronal lesions and, although generalized, was more noticeable in those areas where such changes were present, i. e., the vestibular nuclei and the nucleus rotundus of the thalamus. In addition to this relatively mild type of perivascular change, organizing perivascular hemorrhages were seen later, during the curative stage (fig. 5 *A*).

Severely deficient pigeons which had been treated with thiamine hydrochloride for two to three weeks exhibited further changes. In these birds the vessels in the areas which had suffered parenchymatous degeneration were shrunken and irregular and their adventitia was thickened (fig. 5 *B*). In addition, there were many thick intercapillary bridges (more numerous and thicker than were seen in normal birds).

Studies on Cats.—A. Neuronal Changes: The distribution of such changes in the cat was not studied in detail, but certain general observations were made. A number of kittens were depleted of thiamine more rapidly than we had been able to accomplish in pigeons. They failed to vomit and became prostrate and died in seven to eight days. In these kittens very acute changes were observed in the large ganglion cells throughout the brain (fig. 6 *A*). These changes consisted of chromatolysis, vacuolation, dissolution of the nucleus and, finally, disappearance of the cells, and silver stains indicated that the cell processes and cell bodies frequently degenerated simultaneously. This has been seen in pigeons, but less often (figs. 4 *B* and 5 *B*), apparently because the

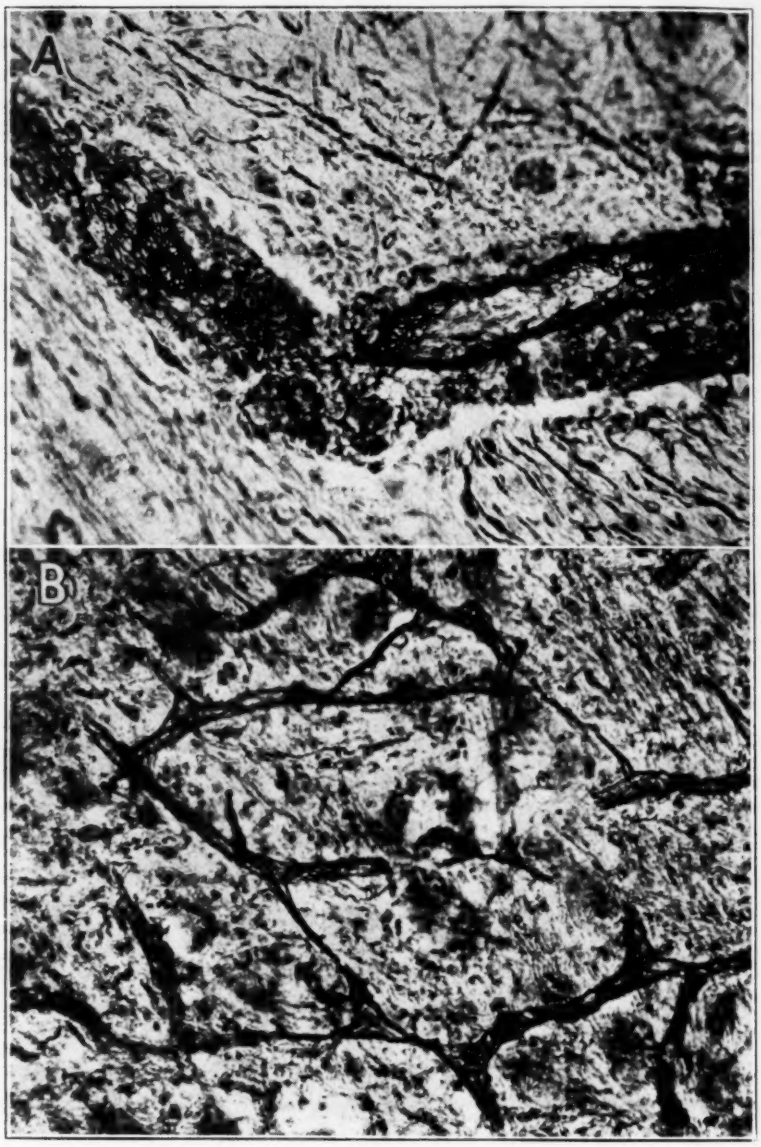

Fig. 5.—*A*, beginning organization of perivascular hemorrhage in the region of the cerebellar nuclei.

B, region of the nucleus magnocellularis in an animal restored to normal. Note the increased connective tissue of the capillaries, their irregularity and the thickened and numerous intercapillary bridges.

Silver connective tissue method; × 444.

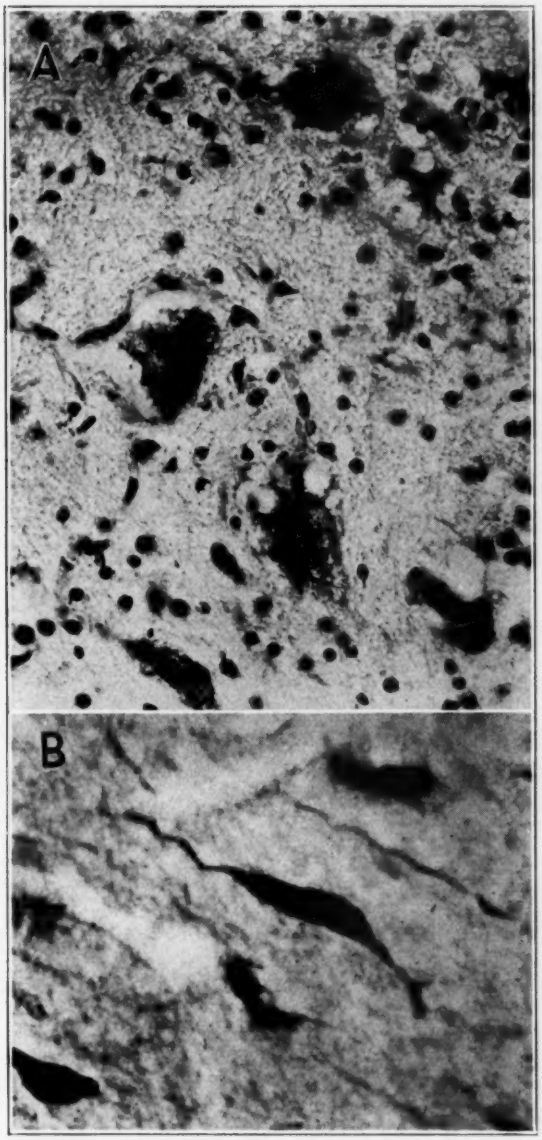

Fig. 6.—*A*, portion of cerebellar nucleus of a very acutely deficient cat, showing acute disease of the nerve cells.

B, portion of cerebral cortex of a kitten with moderately acute deficiency, showing marked sclerosis of ganglion cells.

Nissl method; × 248.

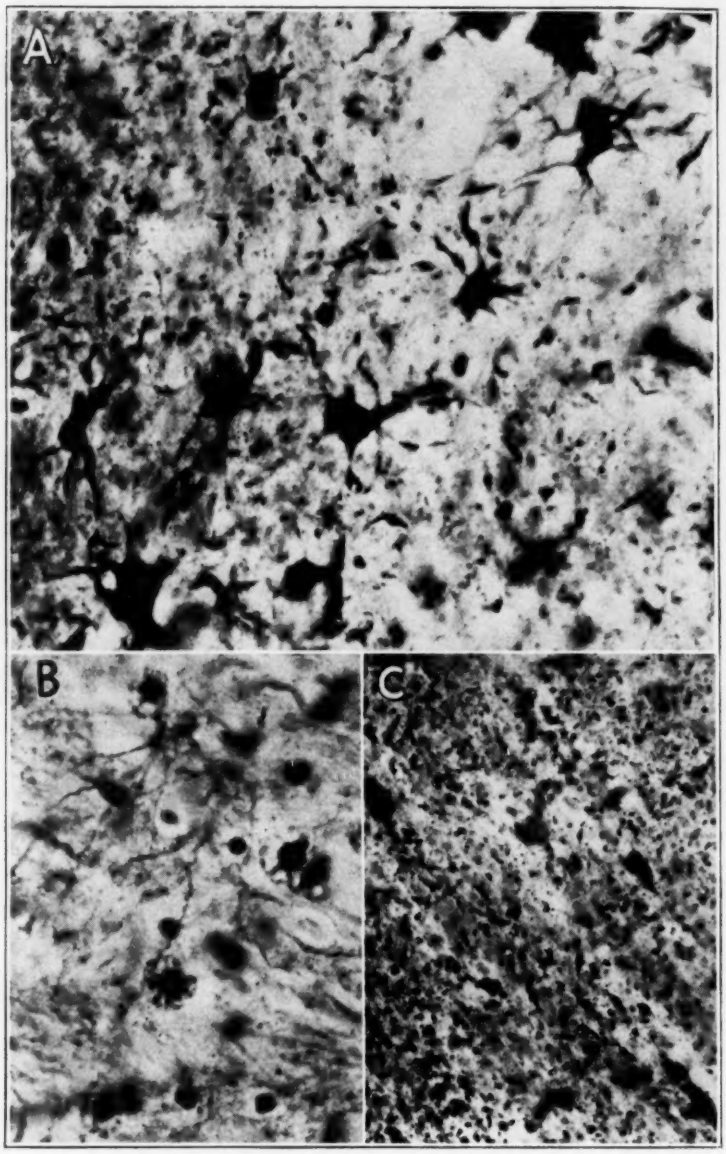

Fig. 7.—Photomicrographs (× 230) of the cerebral cortex of a very acutely deficient kitten. *A*, clasmatodendrosis and pseudoameboid astrocytes (Cajal gold chloride method).

B, acute swelling of oligodendroglia (del Río Hortega silver carbonate method).

C, extreme clasmatodendrosis (Cajal gold chloride method).

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Fig. 8.—Sections of the cerebrum of a kitten with moderately acute deficiency, showing (*A*) gliosis, with hypertrophy and hyperplasia of astrocytes, and (*B*) beginning clasmatodendrosis in the hypertrophic astrocytes.

Cajal gold chloride method; × 220.

pigeons vomited, in this way making the deficiency chronic instead of acute.[6] In less acutely deficient kittens such acute changes were less numerous and many very sclerotic cells were seen in the cerebral cortex (fig. 6 *B*). These changes are more like those that occur in pigeons with moderately acute deficiency.

B. Hemorrhages: These lesions were seen in but 1 of our cats, the one with the most chronic deficiency. These hemorrhages were small and perivascular and were located only in the vestibular nuclei. In this same animal the adventitial changes in the blood vessels were essentially the same as those we observed in the pigeons.

C. Interstitial Cells: In the most acutely deficient cats there was noticeably diffuse swelling of the oligodendrocytes (fig. 7 *B*). Absence of satellitosis indicated that this swelling was not accompanied by an increase in the number of these cells. In these animals the astrocytes, both protoplasmic and fibrous, exhibited very acute regressive changes, consisting chiefly of diffuse clasmatodendrosis (fig. 7 *A* and *C*), to the extent that the fragments of the astrocyte processes (*Füllkörperchen*) were diffusely scattered throughout the parenchyma. The fibrous astrocytes showed less clasmatodendrosis than the protoplasmic type, however; their cell bodies were frequently hypertrophied, and many of their processes were partially present (fig. 7 *A*). These exhibited the well known pseudoameboid cell picture.

In the more chronically deficient cats the oligodendrocytes were slightly swollen or not at all changed. Both the fibrous and the protoplasmic astrocytes throughout the brain showed progressive changes, characterized by hyperplasia and hypertrophy (fig. 8 *A* and *B*). The cell bodies were greatly enlarged and their processes increased in number and thickness. The perivascular glia exhibited a pronounced increase, due to a greater number of astrocytes in this region (Andrienzen cells) and to an increase in the number and size of the vascular feet. This produced a true perivascular gliosis. The numerical increase in the processes of the astrocytes, mainly of the fibrous type, was manifested by the greater number of their vascular attachments, many astrocytes having as many as six or eight vascular feet. One could easily identify the old, hypertrophied fibers and the new, thin fibers. Many of the hypertrophied processes also exhibited very early clasmatodendrosis.

COMMENT

The relation of vascular to neuronal changes was the most striking feature of the present study. Hemorrhages were seen only in regions containing degenerating neurons and were never present in the absence of surrounding parenchymal changes. Since neuronal changes were frequently present in the absence of hemorrhage, we concluded that the

hemorrhages were preceded by parenchymal change. Hyperemia preceded hemorrhage and in cases of severely acute and chronic deficiency had a tendency to spread to areas of the brain in which degenerating neurons were not present. In nuclear regions in which both axons and cell bodies were degenerating, hemorrhages were numerous, whereas hyperemia alone was the predominating feature in places in which only axons and their terminations were affected, i. e., the cerebellum. This quantitative difference could be due to the relative concentration of degenerating tissue in these regions.

The relation of degeneration to the diameter and length of the afferent cell processes has been repeatedly emphasized [7]; the large fibers degenerate first, the smaller ones, later. The same relation of degeneration to the size of the cell body was also noted, and in this study was more clearly demonstrated than before. Thus, the nucleus magnocellularis, which is made up of very large cells, was the first to exhibit both degenerative neuronal changes and hemorrhages. Similar changes appeared soon after in other regions containing large cells, i. e., the cerebellar nuclei, the reticular formation and Deiters' nucleus. This supplies an explanation for the consistency and bilateral nature of the vascular lesions.

We also noted large and confluent hemorrhages with central necrosis in the lateral nucleus of the thalamus and the nucleus rotundus (both nuclei are located in the extreme lateral part of the thalamus), but only in an occasional case have hemorrhages been observed in the paraventricular regions of the thalamus. In the latter region the hemorrhages have always been single and microscopic. Contrary to this, other investigators [3] have stated that large paraventricular hemorrhages occur frequently in thiamine-deficient pigeons, and apparently they have failed to see lesions in the lateral part of the thalamus. Of course, this would make the lesions in pigeons correspond more closely topographically with those observed in human beings with Wernicke's disease. We believe that the topographic distribution of the lesions we have described is the same in the two conditions, although our anatomic interpretation is obviously different. We suggest that sagittal sections of fresh brains, such as Alexander showed in figures 5 and 6 in his article,[3c] are extremely difficult to interpret, since such a soft, small brain (each thalamus is approximately 7 mm. across) cannot be accurately sectioned and many landmarks are lost or distorted. His sections could readily be lateral to the supposed median region. A coronal section (fig. 3 *A*) illustrates the lateral location of the large lesions in our pigeons. In the bird from which this section was taken there was also a very small perivascular lesion in the paramedian region of the thalamus (see arrow). Most investigators seem to have confined their histologic studies to pigeons

with severe deficiency and consequently have failed to observe the earlier lesions.

An explanation for the appearance first of vascular dilatation and then of hemorrhages in the brains of thiamine-deficient pigeons containing degenerating neurons may well be one of local tissue changes, which has been suggested by Church.[2] It is well known that thiamine deficiency interrupts the normal metabolism of carbohydrates, so that pyruvic acid and other intermediary products of carbohydrate metabolism accumulate in the tissues. Now the concentration of these substances would probably be greater in those regions where the impaired metabolism, as evidenced by the degeneration, is most marked. Conceivably, this would lead to local acidosis of those tissues. According to a recent study by Jasper and Erickson,[8] acidosis of the brain leads to an increase in its circulation. It seems reasonable to assume that a similar mechanism operates in thiamine-deficient pigeons, since local vasodilatation occurs in regions which presumably contain a high concentration of acid substances. An increase in the vascular permeability would result in extravasations first of fluid and finally of red blood cells. It has repeatedly been emphasized in this paper that these hemorrhages are localized and preceded by neuronal changes, and are not generalized, as one would expect if thiamine possessed an antiangiodegenerative property, which has been suggested by Alexander.[3c] Furthermore, Tsang [9] has shown that retrograde degeneration in the thalamus and the geniculate bodies results in an increase in the vascular permeability, in the vascularization and in the adventitial connective tissue in these regions.

In acutely deficient cats the swelling of oligodendrocytes and the clasmatodendrosis of astrocytes were probably due to metabolic changes accompanying an acute lack of thiamine. These changes are similar to the very acute degeneration of neurons, which also occurred in acutely deficient cats. In more chronically deficient cats hyperplasia and hypertrophy of astrocytes are more difficult to explain but are probably similar in nature to gliosis, which occurs in the central nervous system after any degenerative process. The proliferation of adventitial connective tissue fibers, the tendency to sclerosis and the increase in intercapillary bridges seem related to the process of repair and generalized atrophy which occurs when neurons degenerate. This general and nonspecific reaction to injury appears in a wide variety of conditions, including

8. Jasper, H., and Erickson, T.: Experimentally Induced Epileptiform Discharge and Its Relationship to Local Changes in Blood Flow p_H and Polarization, Am. J. Physiol. **129**:P390, 1940.

9. Tsang, Y. C.: Vascular Changes in the Lateral Geniculate Body Following Extirpation of the Visual Cortex, Arch. Neurol. & Psychiat. **36**:569 (Sept.) 1936; Vascular Changes in the Thalamic Nuclei Undergoing Retrograde Degeneration, ibid. **44**:1237 (Dec.) 1940.

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experimental thiamine deficiency and Wernicke's disease, and has been described and discussed by many investigators.

The mechanism for the production of hemorrhages in the brains of thiamine-deficient pigeons which we have just described may operate in human brains and be one of the causes of Wernicke's syndrome. It is unlikely that thiamine deficiency is the only cause of this condition, since other deficiencies (either vitamin or cellular chemical mechanisms) may interrupt cellular metabolism and hence may initiate the chain of events leading to hemorrhages. Moreover, it is possible that vitamin C and vitamin K may operate directly on the vascular system in human beings and lead to hemorrhages, as suggested by Minot, Strauss and Cobb.[10] The well known predisposition of vascular lesions to occur in the paraventricular regions, as the result both of trauma and of acutely toxic conditions,[11] might determine the sites of vascular lesions resulting from either of these or from similar causes. It is unlikely that the symptoms of thiamine deficiency are due to hemorrhages, since recovery occurs so rapidly. The ocular symptoms, for example, ophthalmoplegia, are adequately explained by the presence of degenerating neurons in the nuclei of the oculomotor and trochlear nerves. This is supported by the observation that hemorrhages rarely occurred in cats in which prostration and somnolence developed some hours before death (one small hemorrhage in 1 of 13 kittens) and by the presence in these animals of definite acute changes in neurons of the midbrain region and elsewhere.

SUMMARY

Pigeons were made acutely, chronically and very severely deficient in thiamine by feeding by tube a purified diet free of thiamine according to methods outlined before.[12] Kittens were similarly treated. The brains were stained by methods which demonstrate the neurofibrils and chromatin material in the neurons, the perivascular connective tissues and the interstitial tissues.

The vascular lesions were studied in detail. They were preceded by vasodilatation and consisted of perivascular extravasation first of fluid and later of red blood cells. Infiltration of the surrounding tissues followed. The distribution of these lesions corresponded to the distribution of degenerating neurons, as outlined before.[7b] They first appeared in the vestibular nuclei and then spread to other parts of the brain,

10. Minot, G. R.; Strauss, M. B., and Cobb, S.: "Alcoholic" Polyneuritis: Dietary Deficiency as a Factor in Its Production, New England J. Med. **208**:1244, 1933.

11. Chang, Y. C.; Suh, T. H., and Ling, C. C.: Polioencephalitis Haemorrhagica of Wernicke Associated with Febrile Disease, Arch. Neurol. & Psychiat. **45**:658 (April) 1941.

12. Swank and Bessey.[6] Swank and Prados.[7]

notably the nucleus rotundus of the thalamus. Later they appeared in the oculomotor nucleus and the paraventricular region of the third ventricle. Although neuronal lesions were always found surrounding hemorrhages, hemorrhages were frequently absent from regions containing degenerating neurons.

It is suggested that an accumulation in the neighboring tissues of metabolites from interrupted carbohydrate metabolism in the neurons as a result of thiamine deficiency caused the blood vessels to dilate and become abnormally permeable. As a consequence, first fluid and then red blood cells collected in the perivascular spaces.

Proliferation of the adventitial tissues of the small blood vessels and gliosis accompanied the hemorrhages and are thought to be nonspecific reactions to degeneration of neurons (as is seen usually in degenerative processes in the brain).

Swelling of oligodendrocytes and clasmatodendrosis of astrocytes were observed in the brains of kittens with very acute thiamine deficiency in which many necrotic neurons were observed. Presumably, these changes were due primarily to a sudden lack of thiamine. On the other hand, the oligodendrocytes remained relatively unchanged and the astrocytes became markedly hyperplastic and hypertrophied in kittens with chronic deficiency. These changes were considered to be nonspecific and related to the gliosis which occurs when neurons die. Perhaps the products of degeneration furnish the stimulus which causes these changes.

Our observations do not support the thesis that thiamine has specific antidegenerative properties.

CONCLUSIONS

Hemorrhages occur in the brains of thiamine-deficient pigeons and are accompanied by perivascular sclerosis and interstitial cell proliferation. The hemorrhages are preceded by vasodilatation and are first perivascular and later infiltrating. In all instances in our experience the vascular lesions were preceded or accompanied by degenerative changes in neighboring neurons and are thought to be due to metabolic changes in the neurons consequent to thiamine deficiency.

In very acutely deficient kittens acute swelling of oligodendrocytes and clasmatodendrosis of astrocytes were observed, whereas in chronically deficient kittens the oligodendrocytes were slightly, if at all, changed and the astrocytes were markedly hyperplastic and hypertrophied.

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MYASTHENIA GRAVIS TREATED BY EXCISION OF THYMIC TUMOR

REPORT OF TWO CASES

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Since Weigert's [1] discovery of a thymic tumor in a patient who had died of myasthenia gravis, much speculation has arisen concerning the role of the thymus in this curious disease. Postmortem studies disclosed tumors, hyperplasia or enlargement of the thymus in approximately 50 per cent of the cases collected by Norris.[2] It appears likely that this high incidence of pathologic changes in the thymus is more than coincidental.

There are few instances in the literature of successful removal of thymic tumor for myasthenia gravis. Sauerbruch, as cited by others,[3] excised a tumor in 3 cases. Two of his patients died of mediastinitis shortly after operation; the third case is of particular interest here.

A woman aged 20 had pronounced myasthenia gravis and hyperthyroidism. After ten weeks' rest in the hospital her condition remained unchanged. Ligation of the right superior thyroid artery and vein failed to lessen the hyperthyroidism. On the contrary, she became too weak to stand alone or even to feed herself. A few weeks after the polar ligation thymectomy was performed. The gland, which weighed 49 Gm., resembled a fetal thymus. The cortex and the medulla

From the Departments of Neurosurgery, Medicine and Psychiatry of the Albany Medical College and Albany Hospital.

1. Weigert, C.: Pathologisch-anatomischer Beitrag zur Erb'schen Krankheit (Myasthenia gravis), Neurol. Centralbl. **20**:597, 1901.

2. Norris, E. H.: Thymoma and Thymic Hyperplasia in Myasthenia Gravis with Observations on General Pathology, Am. J. Cancer **27**:421, 1936.

3. (*a*) Schumacher and Roth: Thymektomie bei einen Fall von Morbus Basedowii mit Myasthenia, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **25**:746, 1913. (*b*) Adler, H.: Thymus und Myasthenie, Arch f. klin. Chir. **189**:529, 1937. (*c*) Obiditsch, R. A.: Beitrag zur Kenntnis der Thymusgeschwülste im Besenderen derjenigen bei Myasthenie, Virchows Arch. f. path. Anat. **300**:319, 1937.

were differentiated, and many Hassall's corpuscles were seen. No tumor was present. Two weeks after the operation gradual improvement began. Soon she was able to chew and to sit up. Symptoms referable to hyperthyroidism, such as palpitation, became less pronounced. Myasthenic reactions remained. Reexamination eight and fourteen months after thymectomy disclosed improvement both of the myasthenia and of the hyperthyroidism, principally of the former. Sixteen months subsequent to the operation an exacerbation of the hyperthyroidism occurred (increase in the pulse rate, the size of the gland and the exophthalmos). Muscular weakness and fatigue were said to have disappeared by this time. Subtotal thyroidectomy was successfully performed eighteen months after the extirpation of the thymus. We have been unable to learn the subsequent history of this interesting patient.

In a paper dealing largely with the role of the thymus in hyperthyroidism, von Haberer [4] reported the case of a 27 year old man suffering with severe myasthenia gravis, who was treated by thymectomy. Histologic examination revealed that the thymus was in a state of involution. A biopsy of the thyroid disclosed no abnormality. Three years after operation the patient was said to have been much improved. A third case has recently been recorded in an excellent paper by Blalock and his associates.[5]

In this patient, a white woman, myasthenia gravis developed at the age of 16. The first attack lasted approximately three months. During the ensuing four years there were at least three more exacerbations, of increasing severity and duration. Prostigmine was efficacious in relieving symptoms; the amount of the drug required, however, was variable. A roentgenogram of the chest revealed a "sharply circumscribed, dense shadow, just anterior to the left auricle, extending somewhat to the left, but not seen to the right of the midline." At that time roentgen therapy was said to have reduced the size of this shadow. Fifteen months later the mass had grown larger, and subsequent roentgen therapy did not again decrease it.

A few months later (four years after the onset of the disease), when the disease was in a state of remission, the mediastinal neoplasm was removed. This tumor, which was rounded, cystic and smoothly encapsulated, measured 6 by 5 by 3 cm. Histologic examination of the mass failed to disclose any tumor cells within its fibrous tissue wall. Dr. E. W. Goodpasture, summarizing the results of the pathologic study, said: "In attempting to interpret the pathologic picture present, it seems quite likely from the position of the mass and from the clinical relationships that it represents the remains of a necrotic thymic tumor. The necrosis and fibrosis might reasonably be explained on the basis of roentgen ray irradiation." No other tissue suggesting thymus was observed in the mediastinum.

The patient's convalescence was uneventful, small doses of prostigmine methylsulfate having been required for only eight days. During the first year it was

4. von Haberer, H.: Zur klinischer Bedeutung der Thymusdrüse, Arch. f. klin. Chir. **109**:193, 1917.

5. Blalock, A.; Mason, M. F.; Morgan, H. J., and Riven, S. S.: Myasthenia Gravis and Tumors of Thymic Region: Report of Case in Which Tumor Was Removed, Ann. Surg. **110**:544, 1939.

necessary for her to take small amounts of prostigmine bromide on several occasions. In the ensuing four years she has undergone striking improvement and has led a normally active life.

Leriche and Jung [6] published a preliminary case report of a 16 year old girl who had had myasthenia gravis since early childhood. The symptoms had become more pronounced with the onset of puberty, at the age of 11 years. A roentgenogram of the chest revealed no abnormality of the mediastinum. With the use of local anesthesia, thymectomy was performed through a suprasternal incision. No tumor was observed. The gland was lobulated and weighed 16 Gm. Histologic examination revealed that the tissue was lobulated, active, of the infantile type and with no evident fibrosis or fat. Two months later her condition was reported as satisfactory, although little improvement appears to have been observed.

Of 7 patients with myasthenia gravis studied at the Albany Hospital in the past six years, roentgenographic evidence of mediastinal tumor was observed in 3. Of the others, 2 died of their disease. On only 1 of these was an autopsy performed, and no tumor or hyperplasia of the thymus was found. The cases of 2 patients whose thymoma was removed at operation, in 1 successfully, in the other unsuccessfully, are now reported.

REPORT OF CASES

Case 1.—M. F., a white woman aged 45, a school teacher, entered the Albany Hospital May 30, 1939, complaining of fatigability and of difficulty in chewing and swallowing. After an acute infection of the upper respiratory tract five months before admission, the left eyelid began to droop. Soon afterward the left side of the face became weak, especially when smiling or talking. Two months later she experienced difficulty in chewing and swallowing toward the end of a meal, at which time solid food made her choke and fluids regurgitated through the nose. Gradually her speech became thick and of a nasal quality, notably if she conversed more than a few minutes. The right side of the face began to sag, and general weakness of the extremities set in. These symptoms gradually increased in severity, and three days prior to admission she commenced to have attacks of breathlessness, substernal oppression and feelings of suffocation.

The family and past histories were noncontributory.

Physical Examination.—The patient was well nourished, rational, alert and cooperative. The hair was gray. The results of the general physical and neurologic examinations were normal save for the following changes: There was bilateral ptosis of the lids, more marked on the left (fig. 1*A*). No weakness of the extraocular muscles was present at this time. The pupils were equal and reacted to light and in accommodation. The sphincter muscle of the iris could not be fatigued on repeated stimulation by light. The optic fundi were normal. There was no impairment of vision. The expression was masklike, with partial obliteration of the nasolabial folds and drooping of the angles of the mouth. There was profound weakness of the masticatory muscles. It was necessary for

6. Leriche, R., and Jung, A.: Thymectomie dans un cas de myasthénie, Mém. Acad. de chir. **65**:334, 1939.

her to raise her chin with her hand in order to chew or talk. The tongue protruded in the midline, without atrophy or tremor. The gag reflex was hypoactive, but the uvula moved upward fairly well in the midline on phonation. The vocal cords moved poorly. An abnormal amount of rather tenacious mucus was present in the pharynx and larynx. Her attempts to get rid of this were almost constant and ineffectual. Speech was hoarse and indistinct. Only with great effort could she count to 30 or 40. The thyroid was not abnormal. There was no demonstrable widening of the mediastinal dulness on percussion. The superficial and deep tendon reflexes were active and equal, and the latter could not be fatigued by repeated stimulation. There were no pathologic reflexes. There was moderate weakness of the muscles of all the limbs, and this became pronounced on sustained effort. There were no muscular fibrillations.

Laboratory Data.—The hemoglobin was 90 per cent (Sahli); the red blood cell count was 4,610,000; the white cell count was 11,200, and the differential count showed 56 per cent polymorphonuclear leukocytes, 43 per cent lymphocytes and

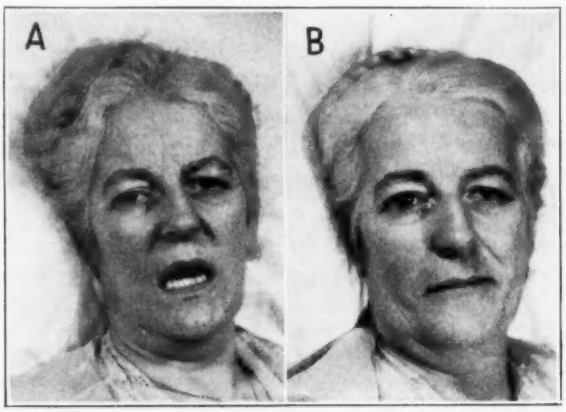


Fig. 1 (case 1).—Photograph of patient (*A*) before and (*B*) one-half hour after 1.5 mg. of prostigmine methylsulfate was given subcutaneously. The partial disappearance of ptosis and recovery of ability to smile and to close the mouth are evident.

1 per cent monocytes. The Wassermann and Kahn reactions of the blood were negative. The urine was normal. The basal metabolic rate was + 10.5 per cent. The daily excretion of creatine in the urine varied from 100 to 730 mg. per hundred cubic centimeters. There was a mild myasthenic reaction to faradic stimulation, but the muscles most seriously involved could not be satisfactorily tested. Roentgen examination of the chest (fig. 2 *A* and *B*) revealed a dense, ovoid shadow extending outward from the rest of the lung on the right side, suggesting a tumor in the anterior portion of the mediastinum. On fluoroscopic examination the mass appeared to be continuous with the cardiac shadow to the right of the midline and to be below and anterior to the lung root. The clinical picture being typically that of myasthenia gravis, it was surmised that this tumor was of thymic origin.

Clinical Course.—The diagnosis of myasthenia gravis was confirmed when dramatic improvement followed the injection of 1.5 mg. of prostigmine methyl-

sulfate and 0.6 mg. of atropine sulfate intramuscularly (fig. 1 *B*). Within fifteen minutes the patient was able to speak clearly and distinctly, to smile, whistle, chew and swallow solid food for the first time in two months. The ptosis disappeared almost entirely except for a slight droop on the left. The feeling of well-being was striking.

It was necessary at first to administer 30 mg. of prostigmine bromide orally six times per day. Six-tenths cubic centimeter of tincture of belladonna was given with each dose of prostigmine. Ephedrine sulfate, 24 mg. four times per day, proved beneficial. After a few days, however, it became apparent that the responses to these drugs were diminishing. Symptoms were less completely relieved. Various other adjuvants, such as potassium chloride, guanidine hydrochloride, amphetamine (benzedrine) sulfate and mecholyl (acetylbetamethylcholine) were tried, without success.

Two weeks after admission it became necessary to increase the dose of prostigmine bromide to 30 mg. orally every two hours from 6 a. m. to 12 midnight (300 mg. daily). With each dose of prostigmine 24 mg. of ephedrine sulfate was given. Even this rather large dose failed to relieve the symptoms completely.

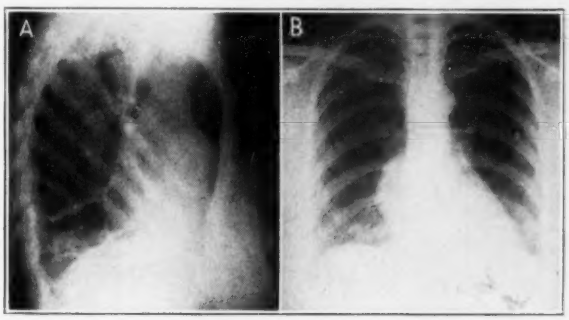


Fig. 2 (case 1).—*A*, lateral roentgenogram, showing thymoma in the anterior portion of the mediastinum. *B*, roentgenogram showing rounded edge of tumor to the right of the heart.

Attacks of dyspnea and palpitation returned. Talking, chewing and swallowing again became difficult. From the twenty-eighth to the forty-second day in the hospital, she was given eight high voltage roentgen treatments of 255 r each (a total of 2,040 r) over the mediastinal tumor, without clinical or roentgenologic evidence of improvement. Her condition became progressively worse (fig. 3), despite administration of 15 to 23 mg. of prostigmine methylsulfate per day intramuscularly. She complained almost constantly of substernal pressure, dyspnea and generalized weakness. Periods of suffocation became frequent and alarming.

Since the foregoing measures had obviously failed to alleviate the symptoms and her condition was now desperate, it was decided to remove the mediastinal tumor.

Operation.—On July 22, 1939 the patient was anesthetized (Dr. F. A. D. Alexander) by administration of cyclopropane through an intratracheal tube, having been given as preliminary medication 8 mg. of morphine sulfate and 0.3 mg. of scopolamine hydrobromide. A horizontal incision was made over the right third rib from the anterior axillary line to the left sternal border. The third rib was resected subperiosteally from the sternal juncture laterally for about 7 inches

(17.8 cm.). The pleura was then entered and the right lung collapsed. There was no apparent reaction to this, the color, pulse and blood pressure remaining good throughout the entire procedure. A self-retaining rib retractor was inserted and the collapsed lung protected with wet Mikulicz pads. The internal mammary artery and veins were cut between silk ligatures. Approximately 1 cm. of the sternal margin between the second and the fourth rib cartilage was rongeured away. The tumor was then in plain view (fig. 4 *A*) and was readily accessible. It was about the size of a large lemon and well encapsulated. It consisted of two parts, the lateral being rounded and fluctuant, the medial solid and rather flattened. The tumor was somewhat movable, particularly laterally, and this surface, as well as the anterior one, was covered with parietal pleura. As shown in the accompanying drawing, the mass overlay the great vessels and the superior anterolateral surface of the pericardium on the right. On further inspection, it was seen to have a vascular pedicle coming down through the superior mediastinum. The tumor was gently retracted to the right with the fingers, and a horizontal incision was made through the pleura just below the pedicle. With long curved scissors the

Fig. 3 (case 1).—Increase in myasthenia six weeks after admission. The photograph was taken approximately forty minutes after administration of 1 mg. of prostigmine methylsulfate subcutaneously.

parietal pleura was dissected off in a line running across the upper pole at the pedicle and continued down along the right side of the tumor. Cleavage was excellent and practically bloodless. Since it was desired to occlude the emissary veins as soon as possible in order to minimize the danger of squeezing material from the tumor, the pedicle was quickly dissected free and clamped, cut and transfixed with silk. Some of the blood vessels were 2 to 3 mm. in diameter. No bleeding occurred. With clamps remaining on the tumor side of the pedicle, the mass was then pulled downward and readily stripped from its bed. The parietal pleura was then completely dissected off. The tumor appeared to be encapsulated everywhere, but on its medial edge it was continuous with a mass of grayish yellow, fatty tissue. This was perhaps 1 or 2 cm. in thickness, occupied the anterior portion of the mediastinum and extended from the upper border of the pericardium up to the innominate vein. It was not unduly vascular. The tumor was somewhat adherent to the pericardium, but fortunately could be dissected off without undue trauma. The whole mass then came away in one piece, without bleeding. All clamped portions of the remaining tissues were transfixed with silk. The patient had not been in any way upset during the procedure, except for a few

moments when traction was at its greatest, at which time there was slight cardiac irregularity. A large biopsy specimen of the adjacent fatty tissue was then taken. In the tumor bed could clearly be seen the ascending portion and the beginning of the transverse arch of the aorta and the superior portion of the pericardium. The phrenic nerve ran perhaps 1 cm. posterior to the margin of the tumor and was not injured. The reflected pleura was next closed with a continuous lock stitch of silk. The chest cavity was reinspected and found to be quite free from blood. It was washed with warm saline solution before closure of the chest wall was commenced. A single sliver wire stay suture was passed around the second and fourth

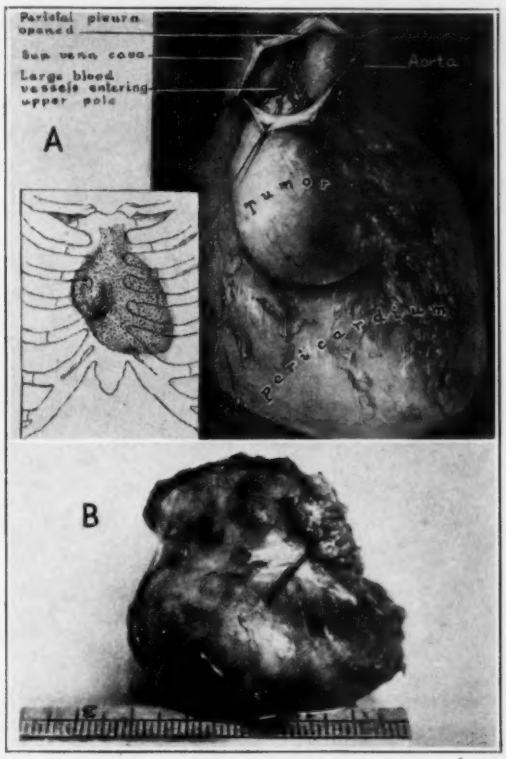


Fig. 4 (case 1).—*A,* drawing of tumor as seen at operation. *B,* thymus after removal. The measure is in inches.

ribs. Before the last silk mattress suture in the pectoral muscles was ready to be tied, the lung was inflated under positive pressure until it completely filled the cavity. The remainder of the wound was closed in layers with interrupted sutures of fine silk without drainage. The patient was returned to her room in good condition.

Pathologic Description of Tumor (Dr. A. W. Wright).—"The specimen removed consisted of a pear-shaped, encapsulated, rather soft, somewhat fluctuant mass, measuring 6 by 5 by 5 cm. (fig. 4*B*). On section it was seen to be cystic and divided into three compartments, separated by fibrous septums. The largest

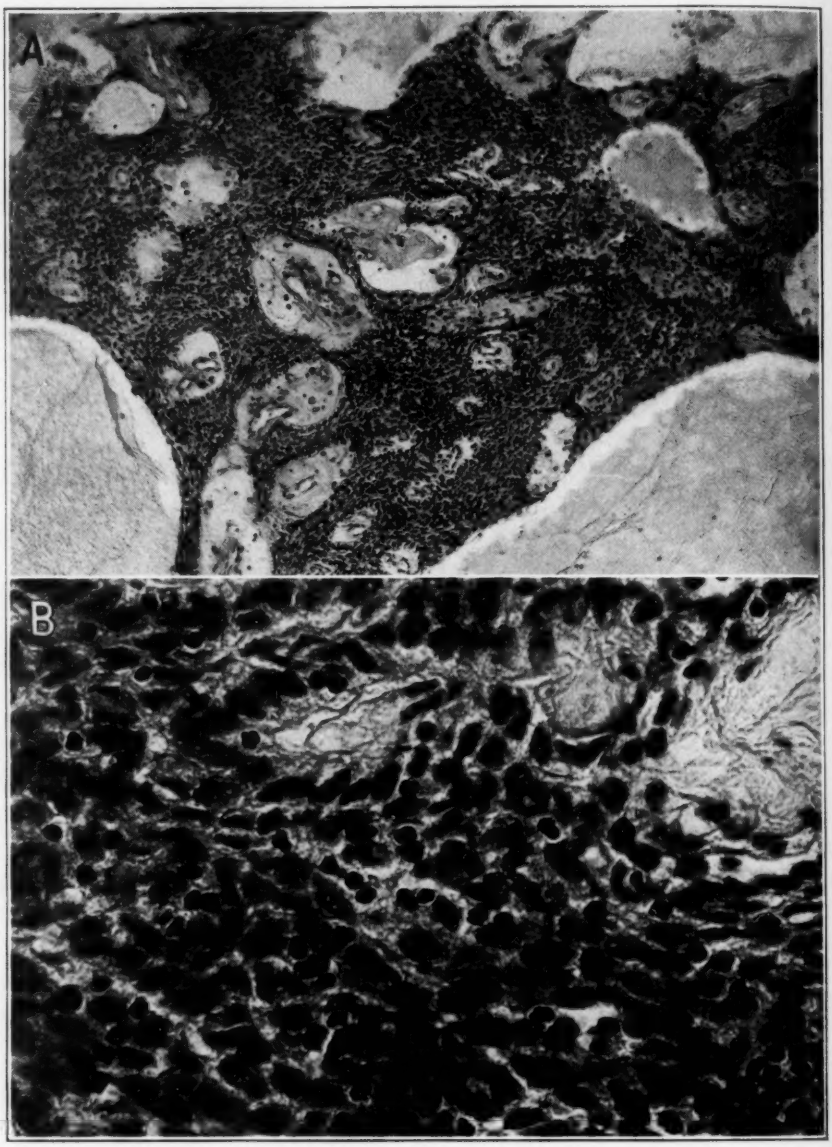


Fig. 5 (case 1).—*A*, low power photomicrograph of thymic tumor, showing anastomosing bands of epithelial cells surrounding fluid-filled cystic spaces. Small numbers of lymphocyte-like cells are still scattered among them. Hematoxylin and eosin; × 130. *B*, high power photomicrograph of the same tumor, showing the character of the epithelial cells, their arrangement about cystic spaces and the lymphocyte-like cells scattered among them. Hematoxylin and eosin; × 730.

compartment contained a gelatinous yellowish material; the other two were filled with hemorrhagic, granular, disintegrating tissue.

Histologically (fig. 5) this mass was a slowly growing, encapsulated cystic neoplasm. The tumor cells were of two types: closely packed epithelial cells, which formed a sort of syncytium, and lymphocyte-like cells, which were irregularly scattered among them. The epithelial cells were long and spindle shaped and resembled those of an adamantinoma. Their cytoplasm was pale staining, often vacuolated, and the nuclei were elongated, vesicular and showed no evidence of

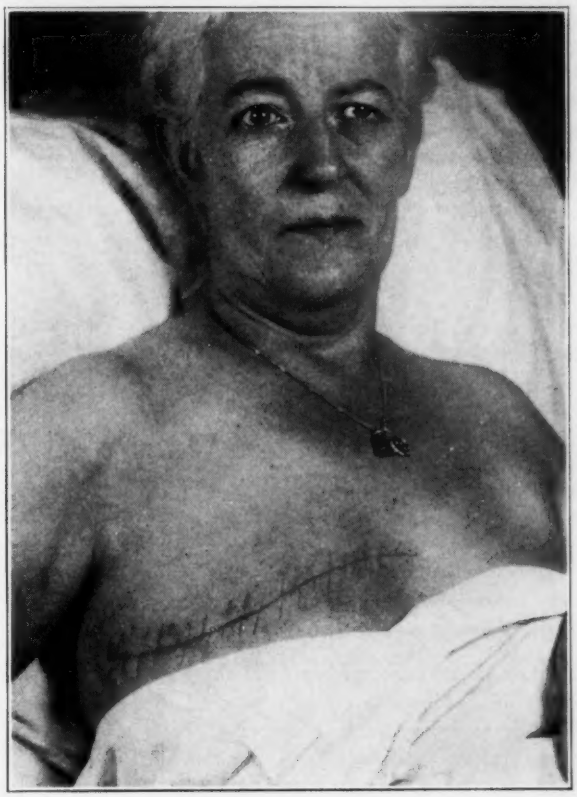


Fig. 6 (case 1).—Condition three weeks after operation. Photograph taken approximately forty minutes after administration of 30 mg. of prostigmine bromide by mouth. The line of incision is evident. Note the residual ptosis in the left eye.

mitosis. These cells bordered small and large cysts, which contained fluid and sometimes fibrin. No Hassall corpuscles were observed.

The lymphocyte-like cells were scattered among the epithelial cells and, as shown in the photomicrographs, stood out sharply because of the hyperchromatic character of their nuclei. These cells resembled thymic lymphocytes.

The tumor was considered to be an encapsulated new growth of thymic origin.

The consensus of a number of eminent pathologists in other cities was that this tumor was of thymic origin.

The cystic fluid and the tumor substance were assayed with use of rats and cats, both in vivo and in vitro, by Dr. Donald McEachern, of the Montreal Neurological Institute, but no evidence of a myasthenia-producing substance was found (personal communication to the authors).

Postoperative Course.—The wound healed per primam. It was necessary to administer intramuscularly 15 to 20 mg. of prostigmine methylsulfate per day for a few days. Throughout the first week the myasthenia was essentially unchanged, the ptosis remained pronounced and she was unable to look upward beyond the horizontal. The mouth could not be closed completely without the assistance of her hand. Nausea, abdominal cramps and excessive salivation continued to be distressing. During the second week improvement gradually became manifest. By the twelfth postoperative day her symptoms were relieved by intramuscular injection of 6 mg. of prostigmine methylsulfate per day. She was able to swallow solid foods with ease; the ptosis was less marked; speech more distinct, and she was allowed to sit up on the edge of the bed. A week later (fig. 6) she was out of bed and walking about. Prostigmine bromide was then given orally in doses of 30 mg. six times daily. Improvement continued steadily. She left the hospital on August 25 and was kept comfortable by administration of 30 mg. of prostigmine bromide and 24 mg. of ephedrine sulfate orally four times per day. Under this regimen the only apparent stigma of myasthenia was slight ptosis of the left lid.

Subsequent Course.—During the following months her strength gradually returned. She was kept comfortable by administration of 4 to 6 tablets (15 mg. each) of prostigmine bromide, supplemented with ephedrine, by mouth The basal metabolic rate was —22 per cent four months after operation. She has menstruated but twice since that time. Mild menopausal symptoms have not been relieved by estrone.

A few weeks after leaving the hospital she was able to do light work about the house. She has since resumed her occupation as teacher of a country school. She continues to take 6 tablets (15 mg. each) of prostigmine bromide per day. At present, two years after operation, her general condition appears to be excellent. It is difficult to judge whether this encouraging improvement is attributable to the removal of the thymoma or a partial spontaneous remission.

Case 2.—S. M., a Jewish housewife aged 52, was admitted to the Albany Hospital on Oct. 1, 1940. She had been in good health until five months previously, when she noticed inability to focus her eyes properly, drooping of both upper eyelids and difficulty in chewing, swallowing and speaking distinctly. These symptoms were observed to improve temporarily with rest. She became progressively worse, diplopia developed, swallowing became very difficult and food regurgitated through the nose. About three months before admission she began to have generalized muscular weakness, associated with difficulty in walking and inability to dress herself without assistance or to hold her head erect. For the previous month she had been practically bedridden.

The family and past histories were noncontributory.

Physical Examination.—The patient was short and obese. Her head sagged forward, with the chin resting on the chest. The face was masklike, with obliteration of the nasolabial folds (fig. 7 *A*). Partial ptosis was present despite bilateral exophthalmos. Except for the abducens nerve, there was complete external ophthalmoplegia. The pupils were equal and regular and reacted promptly to light but sluggishly in accommodation. The fundi were normal. Upward gaze of the

right eye was limited to about 15 degrees; downward gaze, to about 20 or 30 degrees. The patient could not frown or smile, and there was delay in the winking reflex. The tongue protruded in the midline, with some tremor but no atrophy. Speech was thick, nasal and almost unintelligible. Muscle tone in the limbs seemed fairly normal. There was moderate weakness of the upper extremities and shoulder muscles, more pronounced on the right. No atrophy of any muscle groups was observed. The myotatic responses were hyperactive in both lower extremities. The tendon reflexes were equal and active on the two sides. There were no pathologic reflexes. Coordination tests were accurately performed. Abdominal reflexes were not elicited. She walked on a broad base and tired within a few minutes.

The thyroid gland was not enlarged, and there was no lymphadenopathy. To the right of the sternum there was a wide area of dulness, with suppression of breath sounds. Otherwise the lungs were clear and resonant. The heart was normal save for a soft systolic murmur at the apex. The temperature, pulse and respirations were normal. The blood pressure was 160 systolic and 90 diastolic.

Fig. 7 (case 2).—Photographs of patient (*A*) before and (*B*) one-half hour after the administration of 1.5 mg. of prostigmine methylsulfate subcutaneously.

Laboratory Data.—The results of urinalysis were normal. The hemoglobin concentration (Sahli) was 110 per cent; the erythrocytes numbered 6,000,000; the leukocytes, 9,400, and the differential count was normal. The nonprotein nitrogen of the blood was 30 mg. per hundred cubic centimeters, the creatinine 1.4 mg. and the sugar 137 mg. The Wassermann and Kahn reactions of the blood were negative. The basal metabolic rate could not be recorded, as the patient was unable to cooperate satisfactorily. Roentgenograms of the chest (fig. 8 *A* and *B*) disclosed a rounded tumor in the anterior portion of the mediastinum, measuring approximately 7 cm. in diameter. It lay just to the right of the midline and extended into the right lung field, between the third and the fifth costal cartilage. There was a striking similarity in size and location of this tumor to that in case 1. A diagnosis of myasthenia gravis with an associated thymic tumor was made.

Clinical Course.—The patient was given 1.5 mg. of prostigmine methylsulfate with 0.4 mg. of atropine sulfate intramuscularly. Within ten minutes improvement was unequivocal (fig. 7 *B*), and the diagnosis of myasthenia gravis was thus confirmed. Her feeling of well-being was striking; she smiled, nodded, raised her arms

over her head, winked; the diplopia disappeared, and chewing, swallowing and speech were noticeably improved. These beneficial effects lasted approximately an hour.

She was placed on a regimen consisting of administration of 15 mg. of prostigmine bromide, 24 mg. of ephedrine sulfate and 0.4 mg. of atropine sulfate by mouth three times daily. The time of administration was varied according to the needs of the patient. This medication maintained her in a fairly comfortable state. At the end of a week the dose of prostigmine bromide had to be increased to 120 mg. daily. After several days she complained of substernal distress and smothering sensations. During the next three weeks it became apparent that prostigmine was becoming less effective. Other drugs, such as guanidine hydrochloride (10 mg. per kilogram of body weight) and potassium chloride (20 Gm. per day), were administered, without apparent benefit. It became necessary, therefore, to supplement the foregoing regimen with subcutaneous injections of prostigmine methylsulfate (0.5 to 1.5 mg.) two to three times per day. Nevertheless, the myasthenia became more pronounced. Periods in which she felt as

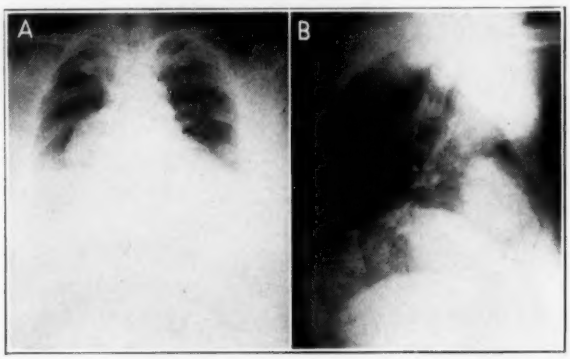


Fig. 8 (case 2).—*A*, roentgenogram, showing thymus at the right of the heart shadow. The right side of the diaphragm is elevated. *B*, lateral roentgenogram, showing tumor in the anterior portion of the mediastinum.

though she were suffocating were now frequent and at times alarming. Since roentgen therapy had apparently been without benefit to the first patient, it was decided (six weeks after admission) to remove the thymoma in this case.

Operation (Nov. 5, 1941).—The patient was anesthetized (Dr. F. A. D. Alexander) by intratracheal administration of cyclopropane, having received 8 mg. of morphine sulfate and 0.3 mg. of scopolamine hydrobromide hypodermically beforehand. An incision was made in the skin overlying the third rib and extending from the right anterior axillary line to the midsternum. The third rib and cartilage were then resected as exposed and therewith a small semicircle of sternum at the chondrosternal junction. The internal mammary vessels were divided between silk ligatures. The right pleural cavity was entered and the lung allowed to collapse. The tumor then came clearly into view (fig. 9 *A*). It was the size of an orange, round, movable and covered with glistening parietal pleura. Its location corresponded with that indicated in the roentgenogram and was almost exactly that of the tumor in the previous case. It overlaid the base of the pericardium on the right as well as the lower portion of the superior vena cava. The

right side of the diaphragm appeared abnormally high and moved little on respiration.

When the pleural covering was reflected, the tumor was observed to be well encapsulated and easily dissected from its loose attachments. The principal blood vessels entered on the posterior medial surface, and not at the upper pole, as in the first case. They were cut between clamps, and the tumor then came away

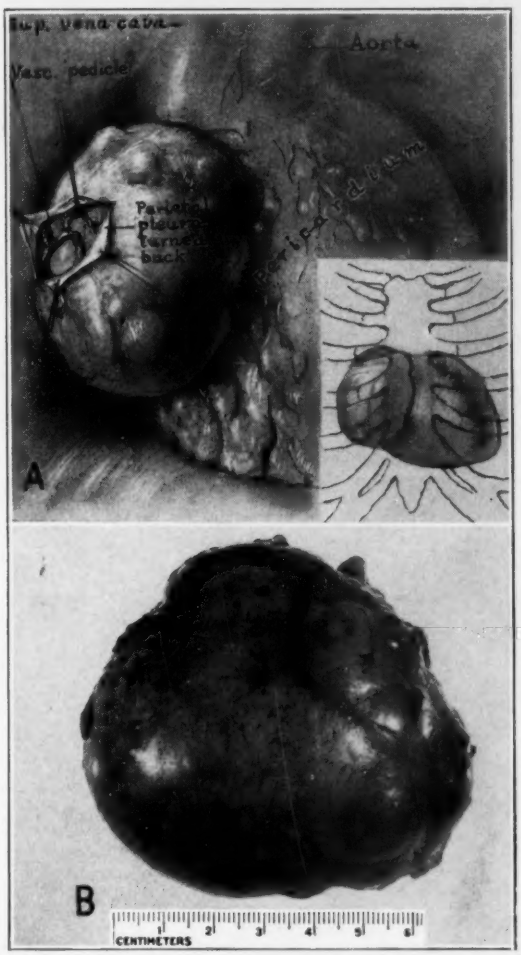


Fig. 9 (case 2).—*A*, drawing of tumor as seen at operation. *B*, photograph of thymoma after removal. It was well encapsulated.

easily and with no evident embarrassment to the patient. The blood vessels were tied with fine silk. No further abnormality could be seen or felt within the accessible parts of the chest. The reflected pleura was closed with mattress suture of silk.

The lung was then reexpanded and the thoracotomy wound closed in layers with interrupted sutures of fine silk. At the close of the operation, which had

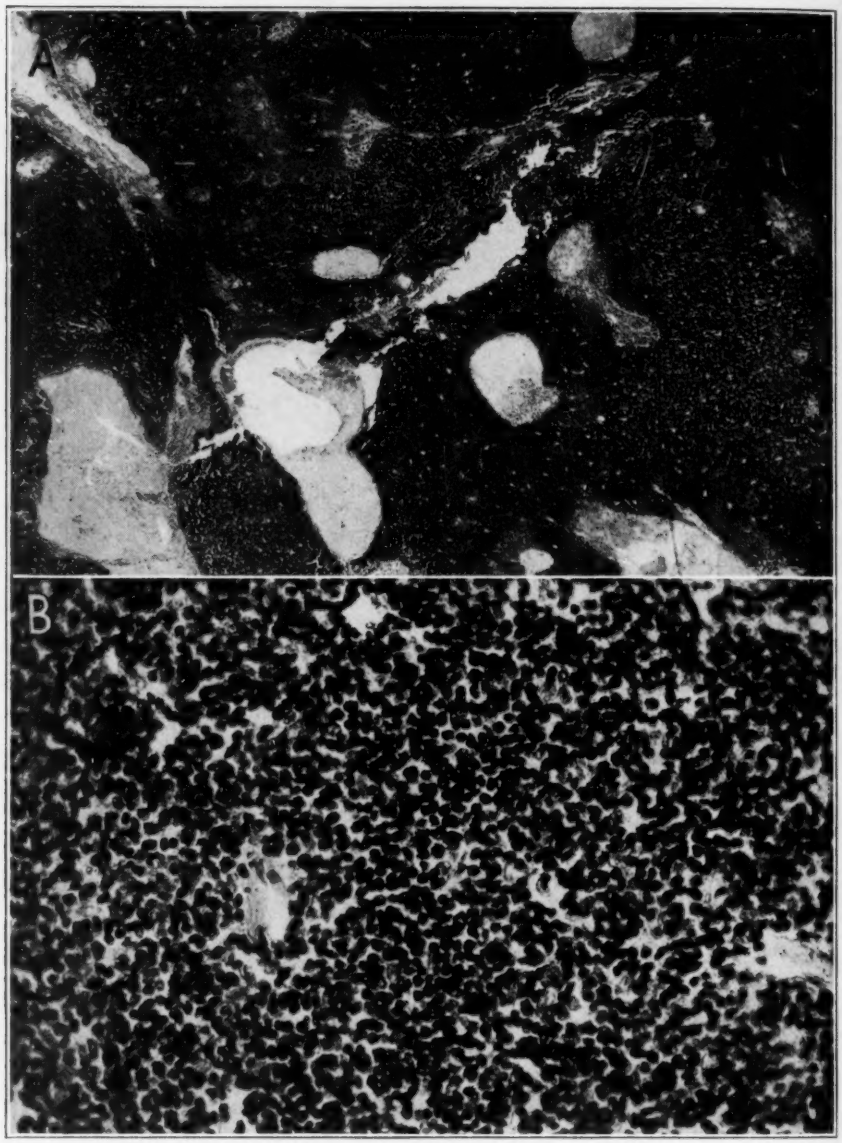


Fig. 10 (case 2).—*A*, low power photomicrograph of thymic tumor, showing the general morphology of the new growth. Several spaces are shown. Hematoxylin and eosin; × 25. *B*, high power photomicrograph of the same tumor. Note the uniform lymphocytic character of the neoplastic cells. Hematoxylin and eosin; × 500.

consumed approximately one and one half hours, the patient's condition appeared unchanged.

Pathologic Description of Tumor (Dr. A. W. Wright).—"The specimen consisted of a firm, smooth, completely encapsulated, ovoid mass (fig. 9*B*), measuring 7 by 6 by 4 cm. and weighing 122 Gm. On section it was found to be a solid, fleshy new growth, grayish pink, somewhat friable and focally hemorrhagic. No cysts were observed grossly.

Histologically (fig. 10) the tumor appeared to be a lymphoma or a benign lymphocytic thymoma. It was completely encapsulated and was composed of masses of small, uniformly sized lymphocytes, supported by delicate fibrous and reticular stroma. Small blood vessels ramified from the fibrous septums into the cellular portions of the growth. Here and there small areas of rarefaction and cyst formation were present, but no epithelium-lined cysts were seen. The small cysts which were present contained fluid, red blood cells and sometimes fibrin strands. Occasional focal hemorrhages were present. Growth of the tumor was slow. No mitoses were seen. Epithelial structures or structures resembling Hassall's corpuscles were not observed in any of the sections."[7]

Postoperative Course.—The immediate postoperative condition was good. Prostigmine methylsulfate and ephedrine sulfate were given liberally by subcutaneous injection. The extraocular movements were normal twelve hours after operation. The following day the patient appeared to be doing well. A total of 6 mg. of prostigmine methylsulfate was administered in scattered doses subcutaneously during the day. Respiration was entirely abdominal. In the evening she became slightly cyanotic, and a hacking, unproductive cough developed. Dulness and suppression of breath sounds were present in the base of the right lung. Her temperature was 99.6 F. per rectum. She complained of smothering sensations. Oxygen was administered continually after operation. On the second postoperative day she suddenly stopped breathing. She responded promptly, but temporarily, to 1.5 mg. of prostigmine methylsulfate and 24 mg. of ephedrine sulfate. She was placed in a Drinker respirator, but became progressively worse and died of respiratory failure about forty-eight hours after operation.

Autopsy.—Examination disclosed partial atelectasis, with early bronchopneumonia in the upper and middle lobes of the right lung. No residual thymic tissue was found in the mediastinum. Both lymphocytic and fatty infiltration were present in the extraocular muscles. The wound was healing normally.

In retrospect it appears likely that bronchopneumonia and atelectasis may have been the principal factors in precipitating the fatal increment of the myasthenia.

COMMENT

Benign tumors and hyperplastic states of the adult thymus are sufficiently rare that an incidence in myasthenia gravis of approximately 50 per cent cannot be ignored.[2] It appears probable that in some manner these thymic abnormalities are related to myasthenia gravis. On the other hand, clinical reports by Viets and Schwab [8] and by Kennedy and

7. This tumor was also assayed by Dr. Donald McEachern, who was unable to demonstrate any myasthenia-producing substance.

8. Viets, H. R., and Schwab, R. S.: Diagnosis and Treatment of Myasthenia Gravis with Special Reference to the Use of Prostigmine, J. A. M. A. **113**:559 (Aug. 12) 1939.

Moersch,[9] based on physical findings and roentgenographic changes alone, suggest that such an association is unusual. However, it must be borne in mind that small tumors, such as one of those described by Miller,[10] might readily escape detection.

It is not yet clear whether thymic tumors, such as those in the 2 cases just described, bear a primary causal relation to myasthenia gravis, similar to the relation of thyroid hypertrophy and hyperplasia to exophthalmic goiter. On the other hand, they might be looked on as secondary or associated, as is the goiter which not infrequently occurs in cases of acromegaly. The available evidence may be summarized as follows:

The remission of symptoms which has been reported to follow thymectomy in the cases of Sauerbruch, von Haberer and Blalock and in our case 1 may be cited as evidence of a primary causal relationship. Although unconfirmed, the experimental work of Adler,[3b] who produced myasthenia in dogs by injection of thymus extract and the relief of these symptoms by administration of prostigmine, is additional suggestive evidence.

On the other hand, it may be equally well argued that these pathologic changes in the thymus are not the cause of the disease, since they are absent in the other half of the cases. Recently we performed an autopsy on a patient who died of myasthenia gravis and, despite a most diligent search, found no abnormality of the thymus. Perhaps of greatest significance is the fact that although the thymoma was completely removed in our first case (M. F.), myasthenia gravis persists, albeit in a milder form. Similarly, in studying the reports of Sauerbruch's and von Haberer's cases one is led to believe that the symptoms of the disease, though lessened, were not entirely abolished.[11] There was apparently no improvement in Leriche's patient after the excision of a hyperplastic thymus. Blalock's patient has been symptom free for five years after removal of the tumor. However, it is interesting to note that this presumable thymoma was so necrotic that no tumor cells could be demonstrated. Myasthenic symptoms had been present even after the tumor had apparently been destroyed by high voltage roentgen therapy. That the removal of this seemingly inert tissue was responsible for the subsequent remission may be considered open to question. It is probably significant that thymic tumors associated with myasthenia

9. Kennedy, F. S., and Moersch, F. D.: Myasthenia Gravis: Clinical Review of Eighty-Seven Cases Observed Between 1915 and Early Part of 1932, Canad. M. A. J. **37**:216, 1937.

10. Miller, H. G.: Myasthenia Gravis and the Thymus Gland, Arch. Path. **29**:212 (Feb.) 1940.

11. There is little reason to believe that myasthenic symptoms persisting after operation result from thymic tissue which is left behind, although the possibility cannot be absolutely denied.

gravis are practically always benign. Malignant thymoma, many cases of which have been reported, rarely,[12] if ever, occurs in conjunction with this disease. Finally, McEachern was unable to demonstrate the presence of any active substance capable of producing myasthenia in animals by extracts or implantations of either of the two tumors which we removed.

The role of thymoma in myasthenia gravis cannot be convincingly established until more patients have been studied for long periods after thymectomy. Remissions in this disease are as well known as those in multiple sclerosis. However, from the observations thus far available, the evidence appears to be slightly against coexistent thymic tumor and hyperplasia being the sole primary cause of myasthenia gravis.

SUMMARY AND CONCLUSIONS

1. The literature containing reports of cases in which myasthenia gravis was treated by thymectomy is reviewed.

2. Two additional cases are recorded. One patient is considerably improved, although mild myasthenic symptoms persist after two years; the death of the other, two days after operation, was partially attributable to bronchopneumonia and atelectasis.

3. Further evidence is presented that benign tumor and hyperplasia of the adult thymus are in some way associated with myasthenia gravis. The results of the studies thus far are insufficient to establish whether this relation is primary or secondary.

Dr. Donald McEachern, of the Montreal Neurological Institute, cooperated in this study.

12. Meggendorfer, F.: Ein Fall von Thymustumor mit vorausgegangen myasthenieähnlichen Erscheinungen, Ann. d. städt. allg. Krankh. zu München **13**:116, 1918. Meister, M.: Lymphoepithelialer Thymustumor und Myasthenie, Klin. Wchnschr. **15**:1389, 1936.

Case Reports

SUPRASELLAR ANEURYSM

Report of a Case, with Recovery

R. M. Klemme, M.D., and R. D. Woolsey, M.D., St. Louis

We wish to report a case of suprasellar aneurysm exposed and incised at operation. A large muscle graft was packed into the aneurysmal sac. This is the sixth instance that we have found of a patient's surviving the opening of a suprasellar aneurysm. Since we have been able to find but few cases of this type in the literature, we wish to emphasize certain aspects of the problem of suprasellar aneurysm both from the diagnostic and from the therapeutic standpoint.

The association of paralysis of the third, fourth, fifth and sixth cranial nerves with aneurysms of the infraclinoid portion of the internal carotid artery has become well known. Dandy [1] has reported several such cases of pure arterial aneurysm diagnosed by clinical means and cured by operation.

A second type of aneurysm has been but little mentioned in the literature. To distinguish this type from the infraclinoid group, it is designated as supraclinoid, or suprasellar, aneurysm. Such an aneurysm may occur at any point on the circumference of the circle of Willis. As may be expected, the symptomatology is grossly different from that usually seen with the infraclinoid type. Whereas the latter causes pressure on the motor nerves to the muscles of the eyeball and on the ophthalmic division of the fifth nerve, the supraclinoid type makes its presence known chiefly by interference with the optic tracts and, secondarily, with the visual fields. Such aneurysms are much less common than those involving the cavernous portion of the internal carotid artery. Jefferson was able to tabulate but 66 such cases from the literature. He also reported 6 cases from his own experience, 4 verified by craniotomy and 2 by injection of thorium dioxide.

REPORT OF CASE

History.—L. R., a 39 year old Polish woman, was referred by Dr. Hedwig S. Kuhn, of Hammond, Ind. The patient was first admitted to the hospital on April 14, 1936, with the chief complaint of headaches of four and one-half months' duration. On Dec. 26, 1935 she had been suddenly seized with a severe headache in both frontal regions as she stooped over to lift an object from the floor. Vomiting followed immediately, becoming so severe that she was confined to bed. At this time paralysis and associated numbness of the right leg were noticed. These functions of the extremity gradually returned to normal during the following week. The headache receded in twenty-four hours, and the patient was able to be

From the neurosurgical service of Roland M. Klemme, Chairman, Division of Neurosurgery, St. Louis University School of Medicine.

1. Dandy, W. E.: Ann. Surg. **107**:654-659 (May) 1938.

up and to carry on her usual household duties. On Jan. 1, 1936 there was recurrence of symptoms with, in addition, a visual disturbance, i. e., inability to see or recognize people about her. Friends told her later that she kept calling for various members of her family and when they appeared she was unable to recognize them. This condition continued until evening, when she awakened from what she called her "trance" and remembered nothing about the whole affair. Speech had been quite normal throughout the attack. On Feb. 6, 1936 the patient had a third episode. She stated that for two or three days she had been losing the vision in her left eye. At first it felt as though there was "something in her eye." There were no further attacks before entering the hospital.

Examination.—The results of the general physical examination were without significance. The blood pressure was 100 systolic and 75 diastolic. Neurologic examination revealed the following positive changes: There was marked pallor of the temporal side of the left optic disk, with no evidence of papilledema. The other cranial nerves functioned normally. There was slight motor weakness of

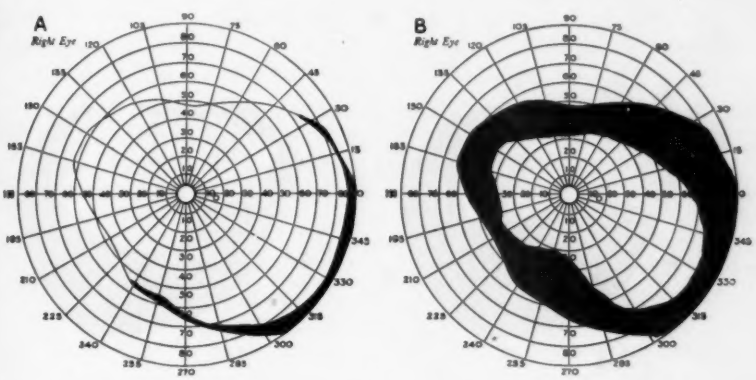


Fig. 1.—Visual fields of the right eye taken with a 0.3 cm. test disk (*A*) on April 15, 1936 and (*B*) on June 20, 1938.

the left arm and hand. Visual acuity was 15/10 + 3 in the right eye; with the left the patient could only distinguish light from dark. The right visual field at that time is demonstrated in figure 1 *A*. Roentgen examination of the skull revealed erosion of the posterior clinoid processes. The sinuses were clear. The basal metabolic rate was —19 per cent. The Wassermann and Kahn reactions of the blood were negative. Examination of the urine and blood gave normal results. The sugar of the blood measured 73 mg. per hundred cubic centimeters and the nonprotein nitrogen, 33 mg. A ventriculogram, taken on April 16, showed that the distribution of air in the ventricular system was entirely normal. The patient was sent back to Hammond, Ind., on April 21, with a probable diagnosis of optic neuritis on the left.

Course of Illness.—During the intervening five years the patient was lost track of, until she finally reappeared at Dr. Kuhn's office in Hammond. A visual field had been taken of the right eye in 1938 (fig. 1 *B*). In addition to the headache, which had become continuous, there was beginning loss of vision in her right eye. She stated she had consulted numerous physicians in the Middle West because

of this, one of whom had performed a thyroidectomy, without affording her any relief. The only change in her symptoms had been marked irregularity in the menstrual periods. At her last menstrual period, for example, the flow was constant for two and one-half months. The menses were copious at times and very scant at others.

Second Admission.—She was readmitted to St. Luke's Hospital in St. Louis on Feb. 7, 1941. Examination at this time revealed a blood pressure of 120 systolic and 70 diastolic. The pupils both reacted to light. The left pupil was larger than the right; both optic disks showed marked pallor. There was still no evidence of papilledema. A suprasternal thyroidectomy scar was noted. The results of other examinations, including the pelvic, were entirely negative. The urine was normal; a blood count revealed 3,880,000 red cells, 80 per cent hemoglobin and 6,500 white cells. The visual field on the right is shown in fig. 2 *A*. A second ventriculogram, taken February 8, revealed that the distribution of air was entirely normal, as at the first examination. Because of increasing loss of

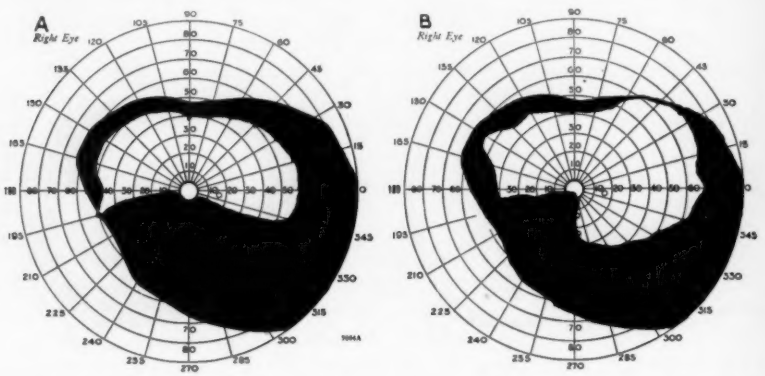


Fig. 2.—Visual fields of the right eye taken (*A*) on Jan. 1, 1941 and (*B*) on June 21, 1941.

vision in her right eye, an exploration of the optic chiasma was advised. On February 15 a craniotomy was done.

Operation (Feb. 15, 1941).—With the patient under anesthesia induced by avertin with amylene hydrate, ether and 0.5 per cent procaine hydrochloride, after preparation with soap, water and alcohol, a unilateral left frontal flap was turned down in the usual manner. The frontal lobe was elevated extradurally to the sphenoid fissure, and the dura was incised. The frontal lobe was further elevated. A large tumor, lying under the left optic nerve and extending back about 1½ inches (4 cm.) toward the parietal lobe, was uncovered. The mass was hard and firm and did not pulsate. Because of this firmness, it was not thought necessary to aspirate the mass. It was therefore incised with the electric knife. A curet was then used to remove the contents of the capsule, which had the appearance of a perineural fibroblastoma. On the third curettement there was a sudden gush of blood, and it was obvious the mass consisted of an aneurysmal sac, containing laminated blood clot. Bleeding was instantly controlled by pressure of the operator's index finger. The internal and external carotid arteries were exposed in the neck, but direct compression of these vessels did not influence the

bleeding when the operator's finger was removed from the bleeding point; consequently these arteries were not ligated. A large piece of muscle was then removed from the thigh and gently teased beneath the operator's finger into the large cavity of the aneurysm. The patient's blood pressure shifted but 15 mm. during this whole procedure, and it was not necessary to give her a transfusion. After waiting for about ten minutes, it was found that the pressure plus the muscle graft had completely stopped all bleeding. The bone flap was then replaced and held securely by using silk for the periosteum. The skin flap was replaced, using silk for the galea and skin. One stab drain was placed under the skin flap. Silver foil, gauze and crinoline dressing were applied. The wounds in the thigh and neck were closed with interrupted silk sutures.

Postoperative Course.—Postoperatively the patient did well. At 10 p. m. on the day of operation she got out of bed, but apparently suffered no ill effects. Sutures and drain were removed after twenty-four hours. Convalescence during the next two weeks was uneventful, except for a slight elevation in temperature from the ninth to the thirteenth day. She was discharged from the hospital on March 13, 1941. The visual field of the right eye taken on June 21, 1941 is shown in figure 2 *B*.

COMMENT

The case history of a patient with a suprasellar aneurysm has been presented. Several features are unique. In the first place, the examinations of the visual fields, extending as they do over a period of five years, provided a record of slow growth of an aneurysmal sac with gradual encroachment on the optic nerves. These fields provide the most important feature of what Jefferson has called the characteristic picture of a supraclinoid aneurysm, i. e., rapidly failing vision in the ipsilateral eye with a superimposed definite homonymous hemianopia in both eyes. Another interesting finding, namely, a large homonymous field defect with atrophic nerve heads, was present. Visual acuity on the left could not be measured. The patient could only occasionally distinguish light. This is a feature which is again common to the picture of supraclinoid aneurysm. As Jefferson stated in his excellent monograph on the subject, "A homonymous field defect with papilledema is a neurological commonplace; the case is far otherwise when the nerve heads are atrophic."

Ventriculographic examination gave us no help in this instance, as the tumor was not large enough to cause compression of the third ventricle. Arteriographic study might have helped, but we have had little experience with this method of investigation and it did not occur to us to subject the patient to this apparently harmless procedure.

We have found but 5 instances in which the patient survived operative opening of such an aneurysm. Jefferson [2] recorded 1 such case and asked charity for the "surgical mandarin" who makes such a seemingly obvious mistake. His patient died suddenly, eighteen months later. A similar case was recorded in 1937 by Henner, Jirásek and Sikl, of Prague.[3] The patient was suspected of having a suprasellar cyst because of optic atrophy of the right optic nerve, constant right-sided headache

2. Jefferson, G.: Brain **60**:444-497 (Dec.) 1937.

3. Jirásek, A.; Henner, K., and Sikl, H.: Mém. Acad. de chir. **63**:577-589 (April 28) 1937.

and a homonymous field defect. The operation resulted in the death of the patient after a few hours. Sosman and Vogt,[4] in 1926, reported a case in which Dr. Cushing deliberately opened an aneurysm and packed it with muscle grafts. The carotid artery was ligated at the time of operation. Eighteen months later the patient was alive and well. As far as could be determined from the history, this aneurysm was of the infraclinoid type. McConnell,[5] in 1937, reported a case in which he opened an aneurysm and packed it with muscle. The patient was still alive two years later. Trevani [6] reported a similar instance in 1932. The carotid artery was ligated in the neck. The patient died five hours later.

The present case presented another noteworthy feature, in that direct compression of the exposed common carotid artery did not serve to stop hemorrhage from the incised aneurysm. The artery was, therefore, not ligated. The operator felt that the aneurysm probably arose from the junction of the left anterior cerebral artery with the circle of Willis. At the time of this communication the patient is alive and well. Her vision has improved in the right eye (fig. 2 *B*).

4. Sosman, M. C., and Vogt, E. C.: Am. J. Roentgenol. **15**:122-134 (Feb.) 1926.

5. McConnell, A. A.: Zentralbl. f. Neurochir. **2**:269-273 (Jan.) 1938.

6. Trevani, E.: Deutsche Ztschr. f. Chir. **237**:534-535, 1932.

HEMICHOREA (HEMIBALLISMUS)

Association with a Pallidal Lesion, Involving Afferent and Efferent Connections of the Subthalamic Nucleus; Curare Therapy

JAMES W. PAPEZ, M.D., ITHACA, N. Y., AND A. E. BENNETT, M.D., AND PAUL T. CASH, M.D., OMAHA

This report deals with an unusual case of hemiballismus in which the jerky, choreiform movements of the left side of the body (hemichorea) persisted in violent form for seven weeks prior to death. For the control of these abnormal movements various drugs were administered, including stramonium and curare. The treatment with curare was deemed advisable in order to check the ballistic movements. A record of the movements was preserved in a moving picture. The case was of such clinical and therapeutic interest that at the time of death an autopsy was secured. It was a surprise not to find a lesion in the subthalamic nucleus of Luys as was anticipated, since lesions of this nucleus have been reported in other cases of hemiballismus. However, a sizable perivascular lesion was observed in the anterior part of the lateral segment of the right pallidum and the neighboring part of the internal capsule (fig. 1, *LE*). This invited a histologic study.

Histologic examination showed that the lesion interrupted a quantity of pallidal efferent fibers which passed down to end in the subthalamic nucleus. A neighboring part of the right frontopontile tract was also involved. Another, smaller perivascular lesion was observed in the prerubral field on the left side (fig. 3, *LE*). This lesion interrupted a part of the crossed fibers coming from the subthalamic nucleus of the right side (*SU*). Thus, the two lesions, though on opposite sides, involved a part of the main afferent and efferent pathways of the right subthalamic nucleus. The nucleus showed no direct lesion but was obviously indirectly affected by the partial loss of its connecting tracts. This was evident from the loss of some of its neuropil (fig. 3, *G*), the presence of gliosis (fig. 4, *G*) and the chromatolysis of some of its cells.

The diagram in figure 6 has been constructed in the horizontal plane to show the affected connections of the right subthalamic nucleus. A synopsis of the clinical history, therapy and histologic observations follows.

REPORT OF A CASE

Clinical History.—L. K., a white man aged 64, a janitor, of Omaha, formerly a shoemaker and farmer, for five years before admission had had diabetes, which was well controlled by insulin. The patient was well and able to do his work as a janitor until seven weeks before death, when he fell about 3 feet (90 cm.) into a stoker hole where he was working. Soon after that he began having jerking, aimless movements of the fingers of his left hand. These movements gradually involved the muscles of the forearm, arm and shoulder and later all the muscles

From the Department of Zoology, Cornell University (Dr. Papez), and the Department of Neurology, University of Nebraska (Drs. Bennett and Cash).

of the left side of the body, including those of the neck and face but not of the eyes, jaw and tongue. The patient was hospitalized for a week and the movements diminished, but after two weeks they began again in more violent form. At this time the ballistic movements spread to the trunk and the left leg. The patient was referred to one of us (A. E. B.) and was sent to the hospital for treatment.

Physical Examination.—Examination disclosed generalized arteriosclerosis with a blood pressure of 140 systolic and 94 diastolic. Some of the peripheral arteries were soft and elastic. Neurologic examination showed normal sensory functions except for diminution of hearing. The outstanding symptoms were slight rhythmic, involuntary movements of the left side of the face and neck, marked rhythmic rolling movements of the left hand, arm and shoulder and moderate ballistic movements of the left side of the trunk and the left hip, leg and foot. Movements of

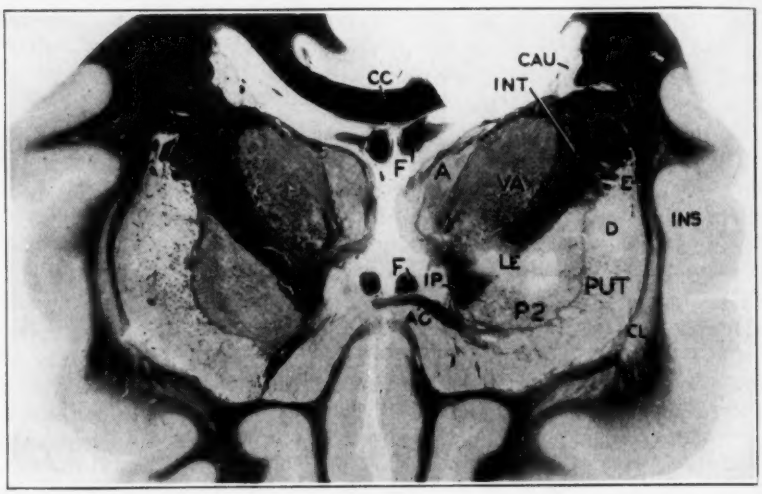


Fig. 1.—Frontal section through the anterior part of the basal ganglia at the level of the anterior commissure (*AC*). It shows the perivascular lesion (*LE*) in the frontal end of the right lateral segment of the pallidum (P_2), extending across the inner part of the internal capsule. There are demyelination and narrowing of the dorsal part of the right putamen (below *E*). Weigert stain; × 1.6.

In this figure and in the accompanying figures, the following abbreviations are used: *A*, anterior nucleus of thalamus; *AC*, anterior commissure; *AMY*, amygdala; *ARC*, arcuate nucleus of thalamus; *B*, lower optic radiation; *CAU*, caudate nucleus; *CC*, corpus callosum; *CL*, claustrum; *CM*, central medial nucleus or centrum medianum; *CR*, conjunctival radiation to ventral lateral nucleus of thalamus; *D*, degenerated fibers; *E*, external capsule; *F*, fornix; *FP*, frontopontile tract; *G*, degeneration of neuropil or gliosis in areas of degenerated fibers; *HA*, habenula; *HD*, hypothalamic descending tract; *HP*, habenulopeduncular tract; *INS*, insular cortex; *INT*, internal capsule; *IP*, inferior thalamic peduncle; *LE*, lesion; *M*, mamillary body; *NR*, red nucleus; P_1, medial segment of pallidum; P_2, lateral segment of pallidum; *PED*, cerebral peduncle; *PS*, pallidosubthalamic fibers; *PUL*, pulvinar; *PUT*, putamen; *S*, strionigral fibers; *SN*, substantia nigra; *SU*, subthalamic nucleus of Luys; *STE*, subthalamicotegmental tract; *SX*, subthalamic decussation; *VA*, ventral anterior nucleus of thalamus; and *VP*, ventral posterior nucleus of thalamus.

the eyes, tongue and jaw were not involved. There was adiadokokinesis on the left side.

Progress of Illness.—The patient was placed under hospital observation. In the arm the constant choreiform, jerky and twisting movements continued. The movements increased on emotional excitement and disappeared during sleep. Stramonium quieted but did not abolish them. Large doses of barbiturates gave the patient but little sleep. Eighty milligrams of curare principle given intravenously or intramuscularly produced complete cessation of the ballistic movements and more marked paresis of the left side of the body than of the right. After curarization the patient was able to get a complete night's rest. The drug controlled the movements more effectively than any sedative or antispasmodic drug that was tried.

The patient gradually became weaker and suddenly died of cardiac and respiratory failure, two weeks after the last admission.

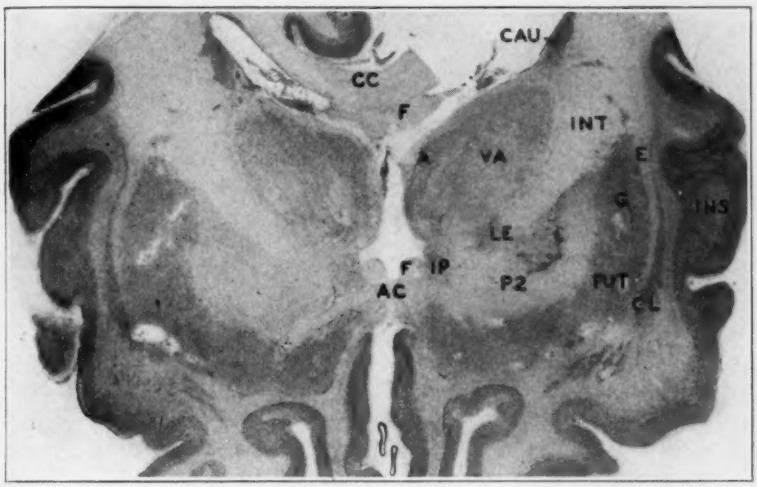


Fig. 2.—Frontal section through site of lesion (*LE*). This shows the perivascular lymphocytosis in the frontal part of the outer segment of the pallidum and the gliosis in the internal capsule and dorsal part of the right putamen (*G*). Cresyl violet stain; × 1.6.

Necropsy.—Examination of the visceral organs showed generalized arteriosclerosis; chronic cholecystitis and fatty degeneration of the liver; fibrosis of the islands of Langerhans; a small adenoma of the right adrenal cortex; a large antemortem thrombus of the left pulmonary artery, and a small thrombus of the right pulmonary artery.

The brain was removed, fixed and cut into several thick slabs by Dr. J. P. Tollman. After further fixation photographic records were made. Shrinkage and depression of the middle of the right premotor cortex (area 6) were noted.

Histologic Examination of the Brain.—The basal ganglia, thalamus and midbrain were cut away from the cortex. They were dehydrated, embedded in pyroxylin and cut into sections 45 microns thick. Every tenth section was stained by a modification (Weil's) of the Weigert method and adjacent sections with

cresyl violet. The series included a total of 240 stained sections. Three lesions were found: one of special importance in the frontal end of the lateral segment of the right pallidum (fig. 1, *LE*); the second, a small one, in the prerubral field on the left side (fig. 3, *LE*), and the third lateral to the posterior part of the right internal capsule (fig. 5, *LE*).

The following histologic criteria were employed. The Weigert sections were used to follow the degeneration and demyelination of nerve fibers and neuropil. The cresyl violet sections were used to show the lymphocytic invasion around the occluded blood vessels, the gliosis of the degenerated tracts and the chromatolysis of nerve cells (especially in the subthalamic nucleus).

The first, and main, lesion (at the level of the anterior commissure) was a large, irregular perivascular lacuna in the anterior part of the outer segment of the right pallidum (fig. 1, *LE*). It surrounded the branches of a small artery,

Fig. 3.—Frontal section through the frontal ends of the red nuclei. This shows the lesion (*LE*) on the left side, in the prerubral field, between the subthalamic nucleus (*SU*) and the red nucleus (*NR*). This lesion interrupted the crossed subthalamicotegmental tract. On the right side demyelination of neuropil (*G*) and fibers (*D*) is seen in the right subthalamic nucleus, as well as demyelination of the frontopontile tract (*FP*). Weigert stain; × 4.4.

parts of which were obliterated. Nearby were dense areas of lymphocytes and some associated mesothelial cells.

The chief destruction was that of the pallidal cells and the efferent fibers from the frontal end of the lateral segment of the pallidum. The tracts left by these partly degenerated and partly demyelinated fibers could be followed in the series down to the place where they perforated the internal capsule (medial border of the cerebral peduncle) and entered the medial part of the subthalamic nucleus. The cresyl violet sections clearly showed the gliosis which followed the degenerated fibers (fig. 2, *LE*).

In the right subthalamic nucleus of Luys changes in neuropil (demyelination) (fig. 3, *G*) and associated gliosis (fig. 4, *G*) were most evident in its medial part.

Since these coincided with the point of entry of the degenerated pallidosubthalamic fibers, the loss of neuropil in the medial part was attributed to their degenerated terminals. In the medial dorsal part of the nucleus there were some demyelination

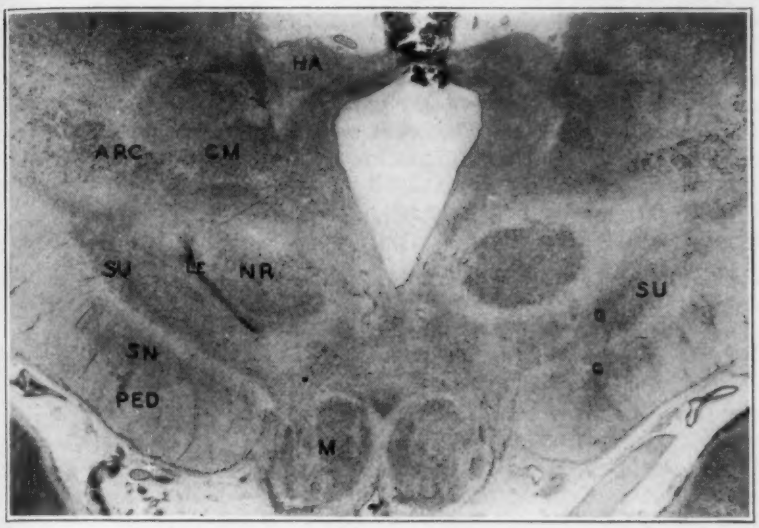
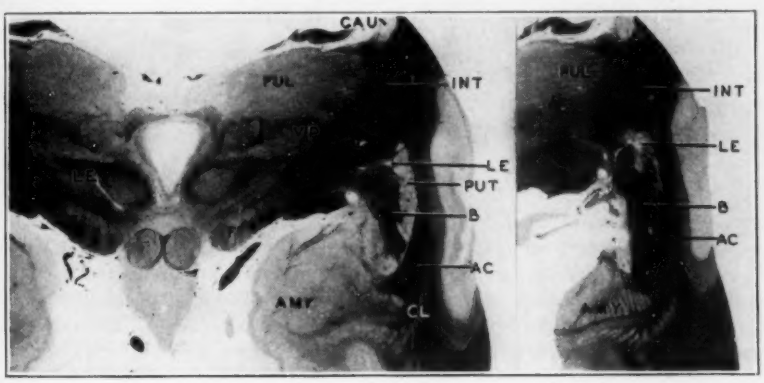


Fig. 4.—Frontal section through level of the red nuclei and the subthalamic nuclei. It shows the lesion (*LE*) with lymphocytosis in the left prerubral field and gliosis (*G*) in the degenerated frontopontile tract and subthalamic nucleus (*SU*) on the right side. Cresyl violet stain; × 4.4.



A B

Fig. 5.—Frontal sections through the level of the pulvinar (*PUL*) and the lower optic radiation (*B*), showing the site of the lesion which damaged the bundle and the adjacent radiations in the pulvinar. Section *B* is caudal to section *A* and shows the greatest extent of the lesion. Weigert stain; × 1.3.

of its efferent commissural fibers (fig. 3, *D*) and sparse chromatolysis of some of its cells. This condition was attributed to retrograde changes caused by the other small lesion on the left side (fig. 4, *LE*).

The second perivascular lesion was on the left side (figs. 3 and 4, *LE*). It was a narrow band situated in the left prerubral field between the frontal tip of the red nucleus (*NR*) and the medial dorsal border of the left subthalamic nucleus (*SU*), but the lesion did not involve directly these adjacent structures.

The artery in the lesion was obliterated and the area was filled with lymphocytes (fig. 4, *LE*). The position of the lesion was directly in the path of the fibers which crossed the dorsal part of the subthalamic decussation (*SX*), just in front of the red nucleus. These fibers evidently came from the demyelinated region (*D*) in the medial dorsal border of the right subthalamic nucleus (*SU*). Below the

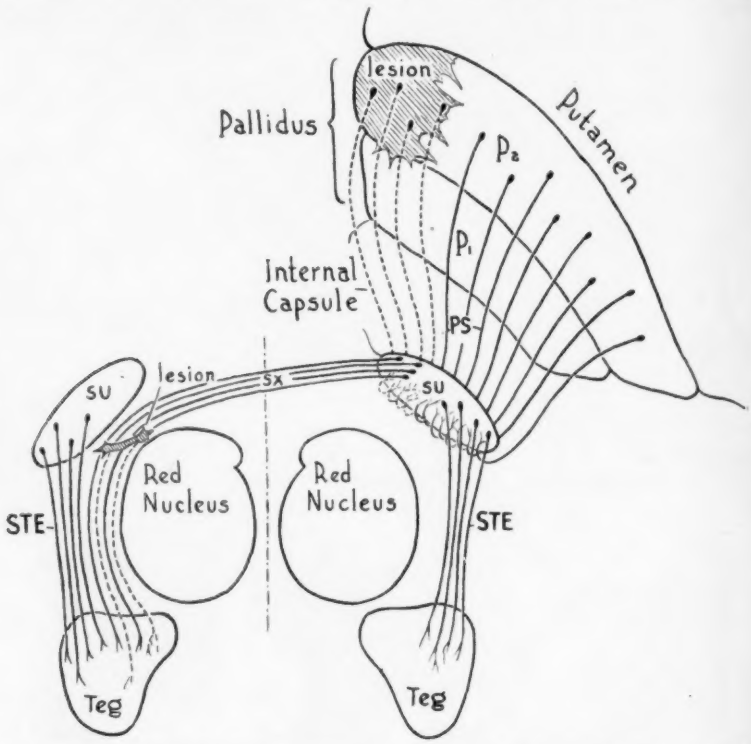


Fig. 6.—Diagram of the topical connections of the outer segment of the pallidum (P_2) with the subthalamic nucleus (*SU*) and the descending subthalamicotegmental tracts (*STE*). The sites of the two lesions are shown, and the broken lines indicate the degenerated fibers, which seem to be absent also in the subthalamic decussation (*SX*).

lesion, on the left side, about one half of these same fibers were apparently degenerated in their downward course. This was apparent from the band of descending gliosis in the position which the fibers normally occupy (by comparison with the normal fibers on right side). The gliosis also extended upward from the lesion, showing that some fibers in the prerubral field and the zona incerta were affected. A slight reduction in density of the prerubral fibers was apparent. The homolateral descending efferent fibers from both subthalamic nuclei were normal and not affected by degeneration.

The third lesion was situated on the right side between the posterior part of the internal capsule and the posterior end of the basal ganglia (fig. 5 *A* and *B*, *LE*). Its chief effect seemed to be on the lower radiations of the pulvinar and the adjacent lower optic radiation. The optic and acoustic radiations were not affected. The lower part of the right pulvinar close to the medial geniculate body had undergone gliosis.

Finally, the first lesion (fig. 1, *LE*) also extended across the adjacent part of the internal capsule (*INT*), where it compromised three sets of fibers: some fibers of the anterior radiations to the frontal cortex, some descending frontopontile fibers (fig. 3, *FP*) and some strionigral fibers related to the dorsal portion of the putamen and the head of the caudate nucleus. All of these minor degenerations could be followed out in the series. The gliosis in the path of the degenerated frontopontile fibers was distinct (fig. 4, *G*). The shrinkage in the right frontal cortex was probably related to this degeneration.

The degenerated strionigral fibers showed lighter staining and a reduction in size. There was a distinct pallor in the dorsal portion of the right putamen; in addition, it was smaller than the left putamen. Gliosis was present in this region (fig. 2, *G*). There was also a slight reduction of the substantia nigra on the right side.

COMMENT

Cases of hemiballismus with lesions in the subthalamic nucleus have been described by Jakob,[1] Martin[2] and others to be mentioned. A number of cases in the literature suggest that very similar symptoms may result from the involvement of fiber tracts above and below the subthalamic nucleus. In the present case the choreiform and ballistic movements of the left side exhibited by the patient appear to have been the result of the lesion in the frontal part of the lateral segment of the right pallidum. This was the largest and the most significant lesion seen in the brain stem.

Ranson, Ranson and Ranson[3] have shown by experiments on the monkey that the lateral pallidal segment sends fibers down to the subthalamic nucleus. A confirmation of this connection was seen in our specimen. Most of the degenerated pallidosubthalamic fibers came from the lesion in the frontal end of the lateral pallidal segment.

Our case brings out the other fact that there is a topical connection between the anterior part of the lateral pallidal segment (which has a medial position, as shown in figure 6) and the medial part of the subthalamic nucleus. The degeneration of the neuropil in the medial part part of the right subthalamic nucleus (fig. 3, *G*), though spotty, was

1. Jakob, A.: Die extrapyramidalen Erkrankungen, Berlin, Julius Springer, 1923, p. 174.

2. Martin, J. P.: Hemichorea Resulting from a Local Lesion of the Brain (the Syndrome of the Body of Luys), Brain **50**:637-651 (Oct.) 1927.

3. Ranson, S. W., and Ranson, M.: Pallidofugal Fibers in the Monkey, Arch. Neurol. & Psychiat. **42**:1059-1067 (Dec.) 1939. Ranson, S. W., and Ranson, S. W., Jr.: The Efferent Fibers of the Corpus Striatum, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:69, 1941. Ranson, S. W.; Ranson, S. W., Jr., and Ranson, M.: Fiber Connections of the Corpus Striatum as Seen in Marchi Preparations, Arch. Neurol. & Psychiat. **46**:230-249 (Aug.) 1941.

clear enough in other sections. The associated gliosis (fig. 4, *G*) indicated that the loss of neuropil was a result of the loss of the pallidosubthalamic fibers. The topical representation in the subthalamic nucleus has been discussed by Martin and Alcock.[4]

The efferent fibers of the subthalamic nuclei have been described by Papez [5] under the name of subthalamicotegmental tracts. They are illustrated in figure 6. The lateral part of each nucleus sends a somewhat separate tract of fibers directly down along its dorsal border. These were not affected. The medial part of each nucleus sends fibers medially into the subthalamic decussation, through which the fibers cross to the opposite side, as seen in figure 3 (*SX*). These crossed fibers pass through the prerubral field, curving in front of the red nucleus. From other normal series cut in various planes it is evident that the crossed fibers pass down along the ventral lateral side of the red nucleus, in close association with the medial lemniscus.[6]

In our case the small lesion in the prerubral field on the left side degenerated a part of the crossed subthalamicotegmental fibers coming from the right subthalamic nucleus. The evidences of neuropathy were definite enough to warrant this conclusion. Martin [2] described and illustrated (his figure 5) such fibers degenerated from a lesion in the homolateral subthalamic nucleus. In our case the homolateral fibers coming from the lateral part of the left subthalamic nucleus were not affected. They were situated to the lateral side of the crossed degenerated fibers. At lower levels in the midbrain all the subthalamicotegmental fibers perforated the medial lemniscus to end in the tegmental nucleus of the midbrain. Just where the degenerated fibers ended was not clear in our series, for gliosis in the tegmental nucleus was slight and diffuse. We have not been able to give these fibers the long course described by Moersch and Kernohan.[7]

Our case answers the question raised by Martin and Alcock [4] whether hemichorea can arise from lesions outside of the subthalamic nucleus. It illustrates well the postulate of Moersch and Kernohan [7] that a lesion might be so situated as to disrupt the functions of the afferent and the efferent fibers of the corpus Luysi, thus producing hemichorea without direct damage to that body. It is further in conformity with the view of Weil [8] that lesions in the basal ganglia may eliminate a path the integrity of which is necessary to the absence of chorea. The view expressed by

4. Martin, J. P., and Alcock, N. S.: Hemichorea Associated with a Lesion of the Corpus Luysii, Brain **57**:504-516 (Dec.) 1934.

5. Papez, J. W.: Reciprocal Connections of the Striatum and Pallidum in the Brain of Pithecus (Macacus) Rhesus, J. Comp. Neurol. **69**:329-349 (Oct. 15) 1938.

6. Papez, J. W.: A Summary of the Fiber Connections of the Basal Ganglia with Each Other and with Other Portions of the Brain, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:21-68, 1941.

7. Moersch, F. P., and Kernohan, J. W.: Hemiballismus: A Clinicopathologic Study, Arch. Neurol. & Psychiat. **41**:365-372 (Feb.) 1939.

8. Weil, A.: A Contribution to the Pathology of Hemichorea, Brain **51**:36-45 (March) 1928.

von Sántha [9] was that to produce hemiballismus the lesion must be in the system related to the corpus Luysi. Alcock [10] stated that it was the fibers of the capsule of the corpus Luysi which appeared to be paler than normal in the 2 cases of senile chorea he described.

From the cases described and reviewed in aforementioned literature there is evidence that lesions of the tegmentum below the level of the subthalamic nuclei may also be responsible for hemichorea (e. g., cases reported by Bianchi [1885] and Bonhoeffer [1897], as cited by Martin [2]).

The pallidosubthalamic fibers on the right and the crossed subthalamicotegmental fibers on the left were involved in our case. Their loss must have in some way altered the normal dynamics of the subcortical motor mechanisms. The choreiform and ballistic movements released by the neuropathy of these fiber connections suggest that the subthalamic system exercises a check or steadying influence on some other constantly dynamic part of the motor mechanism.

The total path of these dynamics is uncertain because the ultimate descending tegmental connections are not clear. Dusser de Barenne [11] has pointed out that the centers controlling posture and progression are essentially subcortical and lie in the brain stem between the levels of the subthalamic region and the medulla (page 229 [11]).

Waller [12] stimulated the region of the subthalamic nucleus and decussation and suggested that the nuclei act as a central device for releasing trunk and limb movements of progression and that they have a bilateral effect. Such a physiologic action suggests that hemiballismus is a symptom of overflow resulting from the loss of normal flow through the connections of the subthalamic nucleus and that an accessory control is involved in production of the movements.

The choreiform and ballistic movements released by the neuropathy of the pallidosubthalamic and subthalamicotegmental tract suggest that this system exercises a check or steadying influence on some other more constantly dynamic part of the central motor apparatus. In this regard one would think of corticospinal, corticopontocerebellar and cerebellodentorubrothalamopallidal (and cortical) pathways. These paths may be regarded as subject to cortical, sensory and cerebellar excitation during wakefulness. This is made likely by the fact that in most cases of hemichorea some degree of voluntary function is preserved.

The sensorimotor cortex is an important excitation field for motor processes. The parietopontocerebellar path may be thought of as holding posture and determining the purposes of movement through cortical

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9. von Sántha, K.: Zur Klinik und Anatomie des Hemiballismus, Arch. f. Psychiat. **84**:665-678, 1928.

10. Alcock, N. S.: A Note on the Pathology of Senile Chorea (Non-Hereditary), Brain **59**:376-387 (Oct.) 1936.

11. Dusser de Barenne, J. G.: The Labyrinthine and Postural Mechanisms, in A Handbook of General Experimental Psychology, Worcester, Mass., Clark University Press, 1934, pp. 204-246.

12. Waller, W. H.: Progression Movements Elicited by Subthalamic Stimulation, J. Neurophysiol. **3**:300-307 (July) 1940.

content. The frontopontocerebellar and the corticospinomuscular paths may be thought of as releasing, patterning and energizing movement.

In our case there was partial degeneration of the right frontopontile tract. The notable shrinkage of the middle (hand) part of the right frontal cortex was probably a result of the degeneration of these fibers. We suppose that this might have contributed to the clinical picture. There were also minor deficits in the left prerubral field, in the right strionigral fibers and in the right anterior thalamic radiations.

SUMMARY

A case of hemichorea of the left side is reported in which curare principle was used to control the spontaneous choreiform and ballistic movements.

Three perivascular lesions were observed, one in the right pallidum, one in the left prerubral field and one in the right lower optic radiation.

The second lesion was in the left prerubral field, directly in the course of the crossed subthalamicotegmental fibers. The subthalamic decussation and a part of the fibers in the right subthalamic nucleus were demyelinated. On the left side a part of the crossed subthalamicotegmental fibers were degenerated below the level of the lesion, as indicated by gliosis.

The first lesion was in the frontal end of the right lateral segment of the pallidum and extended across the internal capsule. It destroyed the medial group of the pallidosubthalamic fibers. It also involved a part of the frontopontile fibers, frontal radiation and strionigral fibers. The subthalamic nuclei were intact, except for loss of myelinated neuropil, gliosis and some loss of cells in the nucleus on the right side.

The third lesion was in the posterior part of the internal capsule and affected a part of the lower optic radiation and adjacent radiations of the pulvinar.

The probable explanation of the hemichorea is the degeneration of the pallidosubthalamic and crossed subthalamicotegmental fibers. The possible routes of the released flow of impulses causing hemichorea are discussed.

News and Comment

ASSOCIATION FOR THE ADVANCEMENT OF PSYCHOANALYSIS

The meeting of the Association for the Advancement of Psychoanalysis will be held at the Copley-Plaza Hotel in Boston on Tuesday, May 19, 1942.

The morning session, at 10 a. m., will be given to a panel on "Human Destructiveness." Participants will be various members of the society and speakers from related fields.

At the afternoon session, at 2 p. m., the following papers will be read:

"Psychoanalysis, Religion and the World Crisis," William V. Silverberg, M.D.

"Evolution of the Neurotic Present from the Traumatic Past," Bernard S. Robbins, M.D.

"The Role of Unconscious Arrogance in Neurosis," Karen Horney, M.D.

"The Role of Instincts in Human Behavior" (a critical review), Judah Marmor, M.D.

"What Is Penis Envy," Clara Thompson, M.D.

In the evening, at 7:30 p. m., the annual dinner for members and guests will be held. There will be dancing.

COURSE OF STUDY IN THE RORSCHACH METHOD OF PERSONALITY STUDY AND CLINICAL DIAGNOSIS

S. J. Beck, Ph.D., head of the psychology laboratory, department of neuropsychiatry, Michael Reese Hospital, will offer his summer course of instruction in the technic of administering the Rorschach test and in scoring of responses. The purpose of the course is to orient the student in interpretation, with especial emphasis on clinical classification. Response records as obtained from various healthy personality groups and from clinical groups will be presented in full, analyzed and interpreted. The accent this year will be on the neuroses.

The course will be in session in 2 two hour periods daily for five days, June 22 to 26, 1942, inclusive. Interested persons are invited to communicate with the medical librarian, Michael Reese Hospital, 2908 Ellis Avenue, Chicago, for further information.

THE LANGLEY PORTER CLINIC

The new Langley Porter Clinic, a 100 bed psychiatric hospital maintained by the California State Department of Institutions in connection with the University of California Medical School and the University of California Hospital at San Francisco, will open on July 1, 1942. This hospital will have an 18 bed neurosurgical ward, a 16 bed children's ward, a series of regular psychiatric wards, an outpatient department, an operating room, an x-ray laboratory and general clinical and research laboratories, including a special electroencephalography laboratory.

The University of California Medical School will be in charge of all teaching and research work. Twelve residencies are available, appointments being for one year. Those appointments coming under the State Department of Institutions carry an allowance of $50 a month plus maintenance for self and family. The maintenance allowance is $60 a month if single and $90 if married, with $5 for each child under 5 years and $15 for each minor child over 5 years of age. Applicants must be graduates of an approved medical school within the last five years and have had at least one year's internship. Appointments are open to both men and women. Applications should be addressed to Dr. Karl M. Bowman, Medical Superintendent, Langley Porter Clinic, the Medical Center, San Francisco.

A NATIONAL COMPETITION FOR AN EMBLEM OF THE AMERICAN PSYCHIATRIC ASSOCIATION

In connection with its forthcoming centenary in 1944, the American Psychiatric Association, Dr. J. K. Hall, Richmond, Va., president, announces a competition for the design of an appropriate emblem. The council of the association entrusted the organization and the general management of the competition to the Committee on the History of Psychiatry. The committee, in cooperation with the Committee on Public Education, Dr. C. C. Burlingame, chairman, has the pleasure of making the following announcement:

Five hundred dollars is available for the distribution of awards. Three prizes of $100 each will be awarded for the three best drawings. The Council of the American Psychiatric Association will then select one of these three drawings which it considers most suitable for its purpose. For this drawing an additional award of $200 will be made. This drawing will become the property of the Association, which will thus acquire all rights of reproduction in any form. All the remaining drawings will be returned.

The designs may be executed in any medium; they should be rectangular and preferably vertical. To facilitate handling, the size of the mat should be 11 by 14 inches. Every care will be taken to prevent injury to the drawings, but the American Psychiatric Association does not assume any responsibility for loss or damage from any cause. The artists are requested not to put their signatures on the face of the drawings, or to place their signatures in such a manner that they may be concealed under the mat. The full name and address of the artist should appear on the back of the drawing.

Drawings should be sent to the American Psychiatric Association, 9 Rockefeller Plaza, New York, and should reach that office not later than April 15, 1942. Regarding all administrative matters please communicate with Mr. Austin Davies, executive assistant of the association, at this address. Inquiries concerning the general ideas of the contest or details of the history or activities of the American Psychiatric Association which might be helpful to the artist are to be addressed to the chairman of the Committee on the History of Psychiatry, Dr. Gregory Zilboorg, 14 East Seventy-Fifth Street, New York. The artist is free to use any idea he deems suitable. It may be suggested, however, that the design represent the aims of the American Psychiatric Association, its purpose in the study and cure of mental diseases and its social and cultural importance. In this respect, the artist may find serviceable an explanatory folder which may be obtained from the office of the association. The jury of selection, which is to choose the three prize-winning drawings, is: Eric Gugler, architect; Leon Kroll, painter, and Paul Manship, sculptor.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

EVOLUTION OF HEMIPLEGIAS IN INFANCY. RANDOLPH K. BYERS, Am. J. Dis. Child. **61**:915 (May) 1941.

Byers calls attention to the fact that the hemiplegia of infancy is usually noted at the time the child begins to walk and that both the parents and the attending physician are apt to say that there was nothing wrong with the child before that time. Frequently a diagnosis of brachial palsy has been made in such cases when difficulty in the use of the arm has been noted, and only later is the cerebral nature of the disease recognized. In a few instances the palsy was noted at birth, but usually it was noted a few days or a few weeks after birth. None of the infants in the series died; therefore no autopsy data are available. An encephalogram in 1 case showed enlargement of the lateral ventricle on the side opposite the spastic extremities, and in 1 case a subdural hematoma was found. In another case, in which the course was similar and the spinal fluid grossly bloody, burr hole exploration revealed nothing abnormal.

According to the author's data, the age at which the paresis was believed to have become spastic and clearly cerebral in origin varied from 6 months to 8 years of age. In most of the cases, however, it was between 6 months and 2½ years. The author believes that in none of the cases presented did any injury to the nervous system occur after the original lesion. Fifteen infants were studied, all of whom showed paresis of one arm early in life, the hypotonia being so pronounced that in several instances a diagnosis of brachial palsy was made. In 14 of the cases later development of spastic cerebral palsy occurred. The author calls particular attention to the report of Langworthy that when very immature animals are decerebrated rigidity does not occur, but that when young animals mature enough to exhibit normal gait and posture are subjected to this operation decerebrate rigidity results. He also points out that Kennard has shown that removal of the motor and premotor cortex of one side in infantile monkeys produces few motor changes. More extensive removal in infancy is followed by weakness of the opposite extremities, and unless very extensive injury occurs, the finer movements of the hand and forearm are the most affected of the voluntary musculature. In 1 of the author's cases recovery followed tapping and removal of subdural fluid. In all the others permanent spastic cerebral lesions developed. In summary, Byers points out that in early infancy weakness and hypotonia are the outstanding features of the hemiplegia. These are most marked at intervals of days, weeks or months after birth, are more obvious in the hand and arm than in the foot and leg and are least evident in the musculature of the trunk. If the involvement is mild, these signs are seen as a disinclination on the part of the child to use the extremity. Later in infancy paresis is replaced by spasticity or the spasticity may appear without recognition of the previous weakness. Byers states that the processes of gradual maturation going on in the brain as a whole are probably responsible for the progressive changes in the picture.

WAGGONER, Ann Arbor, Mich.

NOTE ON THE OXIDATION OF VARIOUS SUGARS BY BRAIN TISSUE. F. BERNHEIM and M. L. C. BERNHEIM, J. Biol. Chem. **140**:441, 1941.

The oxidation of dextrose, mannose, maltose and fructose by washed rat brain suspension is inhibited by iodoacetate, 2, 3, 5-triiodobenzoate and fluoride. Dextrose

and mannose are oxidized more slowly at p_H 6.7 than at p_H 7.8. The reverse is true of maltose and fructose. Both dextrose and mannose can inhibit the oxidation of maltose and fructose.

PAGE, Indianapolis.

THE INFLUENCE OF GROWTH AND MYELINATION ON THE DEPOSITION AND METABOLISM OF LIPIDS IN THE BRAIN. H. WAELSCH, W. M. SPERRY and V. A. STOYANOFF, J. Biol. Chem. **140**:885, 1941.

The deposition and metabolism of lipids in rat brain during early development were investigated with the aid of deuterium as an indicator and by determination of the unsaponifiable lipids and fatty acids. The proportion of hydrogen atoms derived from body water in both lipid fractions, as measured by the deuterium concentration, was highest in the youngest animals studied (4 days old) and declined steadily up to 40 days of age. This result is explained in large part by the fact that with increasing age the absolute amount of lipids deposited in a four day period comprises a smaller and smaller proportion of the total lipids, even during myelination. An additional cause of the decrease in deuterium concentration is a decrease in the rate of regeneration of lipids in the brain with increasing age. Up to 40 days of age growth is quantitatively a more important factor than myelination in the deposition of fatty acids in the rat brain. The quantity of unsaponifiable lipids deposited in the process of myelination appears to equal that deposited as a result of growth at about 20 days of age and to exceed it thereafter. Unsaponifiable lipids, and probably fatty acids, are synthesized in the brain in early life. The rate of regeneration of lipids in the brain appears to be highest during the period immediately after birth, when the demand for lipids for new deposition is also greatest.

PAGE, Indianapolis.

GLYCOLYSIS AND PHOSPHORYLATION IN BRAIN EXTRACTS. S. OCHOA, J. Biol. Chem. **141**:245, 1941.

In the presence of magnesium ions, inorganic phosphate, adenosine triphosphate and cozymase, dilute rat brain extracts form lactic acid at a high rate from added dextrose, hexose monophosphate or hexose diphosphate. In this regard the author's results differ from those of Geiger, who found little lactic acid formation from hexose monophosphate or diphosphate. Dismutation between triose phosphate and pyruvic acid is markedly accelerated in the presence of a phosphate acceptor, such as creatine or dextrose; in this case inorganic phosphate is esterfied, with formation of either phosphocreatine or hexose diphosphate. In aqueous extracts of dry acetone powders of brain, adenosine triphosphatase is completely inhibited by fluoride and the labile phosphate of adenosine triphosphate is transferred to dextrose without liberation of inorganic phosphate (hexokinase reaction). Breakdown of sugar in cell-free preparations of brain occurs after phosphorylation to hexose diphosphate by the same reactions as those involved in similar preparations of muscle, retina and other tissues.

PAGE, Indianapolis.

THE CORNEAL-PTERYGOID REFLEX. A. B. FRENKEL, Vrach. delo **22**:759, 1940.

Frenkel studied the corneal-pterygoid reflex in 967 persons, of whom 747 presented disease of the nervous system, 200 were normal adults and 20 were children below the age of 2 years. In persons with a normal nervous system, in neurotic patients and in those with disease of the peripheral nervous system or of the spinal cord the reflex was only seldom present (6 to 7 per cent) and when present was weak. A clearcut corneal-pterygoid reflex was observed only in the presence of a cerebral lesion. It was present with greatest frequency in syndromes involving the internal capsule or the motor cortical zone. It appears to be associated with a more or less acute lesion of the pyramidal tract. The reflex may be of considerable diagnostic value in cases of cerebral coma, in which it may be active while other reflexes are diminished. The corneal-pterygoid is a reflex involving the trigeminal

nerve, and its reflex arc is normally inhibited by the pyramidal tracts. The reflex is a manifestation of synergism between the eye and the mouth. The functional relation is explained on the basis of the philogenetic existence of a single motor apparatus for the eye and the mouth. This apparatus in a later stage of evolution became separated into two distinct functioning apparatuses, that of winking and that of chewing.

J. A. M. A.

BEHAVIOUR OF MOTOR UNITS IN HEALTHY AND PARETIC MUSCLE IN MAN. HENRIK SEYFFARTH, Acta psychiat. et neurol. **16**:79, 1941.

Seyffarth studied electromyographic records from single motor units. He could find no qualitative differences between functioning motor units in healthy and those in paretic muscles.

BRENNER, Boston.

Psychiatry and Psychopathology

SELF-INFLICTED BULLET WOUND OF FRONTAL LOBES IN A DEPRESSION WITH RECOVERY. ZIGMOND M. LEBENSOHN, Am. J. Psychiat. **98**:56 (July) 1941.

Lebensohn reports the case of a woman aged 49 who four years previously, in the course of a severe depression complicated by alcoholism, attempted suicide by discharging a .25 caliber bullet into her cranium, the bullet entering at a point above and slightly posterior to the outer canthus of the right eye. Rhinorrhea and pneumoventricle followed. At the time of the accident no abnormal neurologic signs were noted. Two months later, however, there were transitory cerebellar gait, hemiparesis with weakness of the facial muscles and rectal and vesical incontinence. The patient's depression disappeared after the accident and has not reappeared. The alcoholism has persisted. Psychologic tests indicate childishness, facetiousness and extroversion. There is no intellectual deficit.

FORSTER, Boston.

PROGNOSIS IN SCHIZOPHRENIA: A STUDY OF 271 CASES. D. SILVERMAN, Psychiatric Quart. **15**:477 (July) 1941.

Silverman made a follow-up study of 271 schizophrenic patients treated in the same institution. About one third (group 1) were treated by individualized psychiatric care and occupational, recreational and physical therapy. One third (group 2) received psychotherapeutic treatment, including psychoanalysis in a few cases. The last third (group 3) included a large percentage receiving shock therapy. Follow-up periods ranged from one to fifteen years, about 97 per cent being observed more than a year. The three groups constituted three chronologic periods, the first being the earliest, with the longer period of observation. The results are summarized as follows: 1. Remissions occurred in 10 per cent of each group. 2. Recoveries (with mild residual symptoms) resulted in 32 per cent of group 1, in 44 per cent of group 2 and in 42 per cent of group 3. Group 3 included more patients with chronic disease. 3. The peak of the recoveries came one to two years after treatment. At the end of this period group 3 led in recovery rate, with 63 per cent. Patients in groups 2 and 3 showed less stable recoveries. 4. Immediate therapeutic results were related to the type of schizophrenia (best results were obtained with the catatonic type), the length of hospitalization, the age (best in the second decade) and the acuteness of onset. 5. The ultimate outcome failed to show the same relation as the immediate results except with respect to catatonia. With respect to age of onset the outlook for the more remote future was most ominous for patients in the second decade. 6. Chronic patients in group 3 were much more responsive than those in group 1. 7. Acuteness of onset was found to be an important prognostic factor. 8. For patients with acute and subacute forms of schizophrenia metrazol and insulin treatment gave excellent results.

SIMON, Middletown, Conn.

PERSONALITY AND HABITUS IN ORGANIC DISEASE. E. DAVIDOFF, E. C. REIFENSTEIN JR. and G. L. GOODSTONE, Psychiatric Quart. **15**:544 (July) 1941.

This study presents an evaluation of some of the factors involved in adjustment to hospitalization for organic disease. Patients representing 100 consecutive admissions to the wards of a general hospital were studied with respect to (1) adjustment to illness and hospital routine, (2) personality integration before hospitalization and (3) anthropometric characteristics. Slightly more than half the patients adjusted well. Of these, the vast majority (about 85 per cent) were found to have well integrated personalities. About one third of the poorly adjusted patients had previously shown well integrated personalities. A general correlation between prehospitalization adjustment and adjustment to physical illness appeared clear. Persons of pyknic build were best integrated and adjusted best to hospitalization but also showed the greater incongruities between expected and realized adjustments. Patients of the dysplastic type made the poorest prehospital and intrahospital adjustments.

SIMON, Middletown, Conn.

A PSYCHOANALYTIC STUDY OF A CASE OF EUNUCHOIDISM. HUGH T. CARMICHAEL, Psychoanalyt. Quart. **10**:243, 1941.

Carmichael analyzed a man of 31 who suffered from eunuchoidism, in order to answer the following questions: What are the effects of gonadal insufficiency on the psychosexual development and on the personality? Will these effects be apparent during childhood, or will they be manifested only after puberty? To what extent will successful treatment by endocrine products influence the behavior?

The analysis showed that the patient had progressed through the usual phases of psychosexual development in childhood up to the phallic phase, which coincides with the height of the oedipus complex and castration fear. His solution of these conflicts was not unusual. His growth was abruptly interrupted at puberty, and he did not attain the genital level. His reaction to this failure of growth consisted in an intensification of the defense measures necessary to meet the greatly increased threats of his phallic organization. The analytic material confirms the view that the weakness of his libidinal drives rendered him incapable of dealing with these problems in a real and satisfactory way and forced him to adopt new methods of ego defense. These defenses were later intensified and added to by real events of a traumatic nature to him, for example, by his father's death. During the long period of years from puberty to the time of successful endocrine treatment he continued in general to manifest the same defense mechanisms. This served to fix these into a rigid pattern. When he attained physical sexual maturity at the age of 30 and the sudden increase in libidinal tension made new internal demands on him, he found himself greatly handicapped by his inability to discard these long-continued methods of defense. The latter tended to repeat themselves in spite of his conscious desire for a new level of adjustment.

Sexual development had been adequate in his childhood. At puberty his failure to grow resulted in his being unable to progress to the genital stage of development.

PEARSON, Philadelphia.

A CHILD ANALYSIS. AGNES B. GREIG, Psychoanalyt. Quart. **10**:395, 1941.

Grieg reports the detailed psychoanalysis of a 9 year old boy to substantiate her belief that child analysis is not different from adult analysis. The only difference lies in the fact that the child ordinarily is more active and less articulate than the adult. Her patient, however, was as intensely inhibited as any adult and therefore began with words, using play only as he became freer.

She points out that there are four factors significant in the analytic relationship which are applicable to everyday child-adult relations. 1. It seems not to matter

much whether a normal child is given specific sex information, if without anxiety he is made to feel free to follow his own impulses in a satisfactory way, either directly or in a substitutive form. 2. It is important to let the child alone when he does not indicate need for help. While things are going well he needs no help and prefers to work things out by himself. Education should be a guiding of creative impulses, and that is possible only where there is considerable freedom of action. There is commonly too much insistence on rules of technic, too much helping and criticizing the child, with the result that potentialities are frequently crushed. 3. The free use of humor makes it possible to approach new material which would otherwise hold intolerable anxiety and also in reducing and constantly draining off fear of the analyst. This relieves the analyst's anxiety, as well as the patient's, and, for the same reason, its cultivation would seem to be valuable in any relationship between child and adult. 4. The analyst goes on guard for the patient, holds off the enemy so to speak, thus allowing him to throw off his armor and be free to live out his fantasies, stopping from time to time for the reassurance that the analyst is still there, still friendly and serene. It is not necessary to understand completely, and certainly at times not necessary to understand at all, what is actually going on, but if the analyst is not anxious neither will the child be. The parent or educator in his insistence on too much supervision, too much prying into the child's affairs, may well cease to be a protector and become a persecutor.

PEARSON, Philadelphia.

ANOREXIA NERVOSA. J. V. WALLER, M. R. KAUFMAN and F. DEUTSCH, Psychosom. Med. **2**:3 (Jan.) 1940.

The syndrome of anorexia nervosa usually occurs in females between 12 and 21 years of age. It is characterized by anorexia, loss of weight, cachexia, constipation, weakness, irritability and amenorrhea. The modern point of view favors a psychogenic origin of the syndrome. Analysis of cases in the literature reveals a typical neurotic pattern of emphasis on food, alternate overeating and undereating, conflict with the family, especially the mother, and, finally, precipitation of the syndrome at the time of adjustment to adulthood. The authors relate this neurotic pattern to the infantile origin of psychopathologic reactions to food, emphasizing that these reactions are based on elaborate symbolizations assumed by the utility function of eating. In the neurotic adolescent repressed fantasies of oral impregnation reappear and evolve into a typical personality reaction in which genital fantasies or activities arouse guilt, disgust or anxiety. Dependent on the amount of guilt and anxiety and aggressions within the family, there may be complete rejection of food, which is understandable in terms of its symbolic significance. The parental role of the mother in relation to eating seems especially important in cases in which anorexia nervosa develops. The mother either overemphasizes feeding or uses this function as a basis for disciplinary measures. The increased fluid intake characteristic of the syndrome is explainable on the basis of an obsessive cleaning and purification ritual. Constipation symbolically becomes equated with the pregnant abdomen and, depending on a shift in neurotic factors, may alternate with diarrhea. Amenorrhea is in keeping with the knowledge that temporary cessation of menses in young women is frequently due to fear of pregnancy. The personality structure in 2 cases reported by the authors was of the compulsive-obsessive type. The environment and fantasy life were remarkably similar. In both there was rivalry with the mother for affection of the father. Oral impregnation fantasies were clearly observed in both cases. On the basis of their studies the authors suggest that the psychosomatic syndrome of anorexia nervosa in its main features represents a somatic expression of the specific fantasy of oral impregnation. Eating is a denial of the wish and an acting out of this fantasy at an unconscious level.

SCHLEZINGER, Philadelphia.

DISORDERS OF MENTAL FUNCTIONING PRODUCED BY VARYING THE OXYGEN TENSION OF ATMOSPHERE. A. L. BARACH and J. KAGAN, Psychosom. Med. **2**:53 (Jan.) 1940.

Barach and Kagan studied the mental reactions of 17 medical students and 9 psychoneurotic patients exposed to an atmosphere containing 13 per cent oxygen, corresponding to the concentration at an altitude of 12,400 feet (3.7 kilometers), for three hours. The medical students showed marked changes in affective behavior, with initial elation in 59 per cent but terminal lethargy in all. The patients revealed an even more marked lack of emotional restraint. The "retention and recall" test showed a larger incidence of errors with impairment of memory in the student group, while in the patient group there was relatively improved performance in 5 of 9 patients. The latter result is considered to be due to freedom from usual preoccupations. The student group revealed only a superficial change in the Rorschach test. The authors conclude that the inhalation of an atmosphere with moderately reduced oxygen concentration for three hours causes an emotional release, with diminished reason, memory and judgment.

SCHLEZINGER, Philadelphia.

AUTONOMIC AND RESPIRATORY RESPONSES OF SCHIZOPHRENIC AND NORMAL SUBJECTS TO CHANGES OF INTRAPULMONARY ATMOSPHERE. H. FREEMAN and E. H. RODNICK, Psychosom. Med. **2**:101 (April) 1940.

Freeman and Rodnick studied the heat-regulating mechanism through suppression of heat loss from the lungs by the inspiration of oxygen heated to 41 C. and humidified to the saturation point. Their subjects were 31 normal persons and 29 schizophrenic patients. As indicators of the degree of reactivity of the autonomic nervous system they selected blood pressure, heart rate, galvanic cutaneous resistance and rate and amplitude of respiration. Comparison of normal and schizophrenic subjects under basal conditions disclosed no striking differences. However, during the experimental period of stress the control subjects reacted with significantly larger cardiovascular and respiratory responses than did the schizophrenic subjects. These results tend to support the concept that the schizophrenic patient is deficient in the adaptability of the autonomic nervous system.

SCHLEZINGER, Philadelphia.

INFLUENCE OF THE EMOTIONS UPON ESOPHAGEAL FUNCTION. W. B. FAULKNER JR., F. H. RODENBAUGH and JOHN R. O'NEILL, Radiology **37**:443 (Oct.) 1941.

Faulkner, Rodenbaugh and O'Neill show that emotional disturbances may produce esophageal dysfunction which is demonstrable both by esophagoscopic and by roentgenographic methods. This was first noted in a routine fluoroscopic examination of a patient with severe esophageal spasm. The spasm disappeared when a chance statement was made which pleased the patient, while an opposite trend of conversation reelicited it. The process was repeatedly carried out, the spasm being elicited and made to disappear by appropriate emotional suggestions.

Twenty-five patients with similar esophageal dysfunction who were responsive to psychosomatic stimuli have been encountered. The authors describe in detail 4 cases in which the changes were essentially the same as in the first case and state that the other cases in their series gave similar histories. These changes could all be demonstrated by esophagoscopic and roentgenographic means.

The examination should be repeated if no roentgenographic abnormality has been noted and the symptoms persist. In cases in which the roentgenographic diagnosis is doubtful the patient should have an esophagoscopic examination; in fact, it is wise to subject to such a study all patients with a condition of this kind in order to exclude the presence of an organic lesion.

KENNEDY, Philadelphia.

PERSONALITY CHANGES IN ADOLESCENCE. MARGUERITE HERTZ and ELIZABETH BAKER, Rorschach Research Exchange **5**:30 (Jan.) 1941.

Seventy-six adolescents were tested at 12 and again at 15 years of age. The authors conclude that the 12 year old child tends to engage less in inner living and fantasy life and responds more readily to the world about him. He tends to be livelier, more "labile" than stable, more excitable than controlled, more "outward" in his emotional behavior. Extroversive elements dominate the personality. By 15 years of age both boys and girls appear more introversive. The 15 year old adolescent tends to withdraw within himself. He is more creative. General responsiveness to the environment decreases. Fewer infantile patterns show, with less egocentricity and impulsiveness and fewer outbursts. There is a definite increase in emotional adaptability and stability.

MARCOVITZ, Philadelphia.

THE STABILITY OF THE RORSCHACH METHOD AS DEMONSTRATED IN ELECTRIC CONVULSIVE THERAPY CASES. DOUGLAS MCG. KELLY, HELEN MARGULIES and S. EUGENE BARRERA, Rorschach Research Exchange **5**:35 (Jan.) 1941.

This study was made on a group of 12 patients who showed complete amnesia but no confusion after electric shock treatment. Rorschach responses were compared before and after treatment. Of 18 other patients not included in the study, 5 had no amnesia and 5 partial amnesia and 8 showed confusion. The Rorschach tests were taken within two hours of each other, and none of the patients showed any significant psychologic change after a single shock. In general, in every test the Rorschach responses were unchanged before and after the shock, and the Rorschach diagnosis coincided with the clinical impression.

All areas and determinants were stable. Those showing most variation were the total number of responses (R), the large details (D), the form percentage (F%), the percentage of responses in cards VIII, IX and X and the popular responses (P). Since these determinants seem to be more labile, it is felt that they are less important from a quantitative point of view than the other determinants. From this study the authors conclude that the Rorschach method is fundamentally reliable and that it measures the same portion of the personality with the same results even when the patient has lost the function of recent memory recall.

MARCOVITZ, Philadelphia.

A STUDY OF SPECIFIC DATA IN THE LIVES OF ONE HUNDRED AND EIGHTY-THREE VETERANS ADMITTED TO ST. ELIZABETHS HOSPITAL. ALEXANDER SIMON, MARGARET HAGAN and ROSCOE W. HALL, War Med. **1**:387 (May) 1941.

Of 183 men admitted to St. Elizabeths Hospital from the Army, Navy, Marine Corps and Coast Guard, 42 per cent broke down within the first six months of their service, 10.3 per cent had had a psychosis prior to enlistment, 8.3 per cent had a record of antisocial behavior, 19.4 per cent had indulged excessively in alcohol, 6.6 per cent were morons, 33.9 per cent had a history of psychosis in one or more members of the immediate family and 37.3 per cent came from broken homes.

The authors believe that draft boards should obtain correct answers to the following questions: 1. Has the patient been treated for nervousness? Has he had a nervous breakdown? Has he been a patient in a sanatorium or in a hospital for the treatment of mental illness? 2. Has he ever had fainting spells? Spasm? Fits? Convulsions? Falling-out spells? 3. Has he ever been arrested? Has he been in a detention home or a training school? A reformatory? A jail? For what? 4. Does the patient drink? How much? How often? 5. What grade did he reach in school? Did he ever repeat a grade? At what age did he leave school? 6. What is his occupation? What is the longest time he kept one job?

7. Has any close relative—a parent, brother, sister, uncle or aunt—ever had a nervous breakdown or been a patient in a hospital for persons with mental disease? 8. Are the parents living? Living together? How old was he when one or the other died or when they were separated or divorced?

PEARSON, Philadelphia.

Diseases of the Brain

NEUROLOGIC SYMPTOMS OF UVEOPAROTID FEVER. P. OTTONELLO and T. ANARDI, Riv. di pat. nerv. **56**:185 (Sept.-Oct.) 1940.

Ottonello and Anardi report the case of a woman aged 58 who, without any prodromal symptoms, exhibited total paralysis of the left facial nerve. This was followed in two days by transient slight bilateral swelling of the parotid gland. Total paralysis of the right facial nerve and disturbance of deglutition and function of the vocal cords appeared one week later. Inflammation of the parotid gland became manifest one month later. Anisocoria and pupillary rigidity appeared in forty-five days and acute polyneuritis of all four extremities in seventy-five days. The deep reflexes disappeared in the course of the disease, and signs of involvement of the cardiac fibers of the vagus nerve became evident. The lymph nodes were not enlarged, with the exception of the hilar nodes, which showed moderate enlargement. All the symptoms but the left facial paralysis disappeared within five months. The tuberculin cutaneous test and the examination of the sputum for tubercle bacilli gave negative results. The cerebrospinal fluid exhibited changes of a meningeal character, slight lymphocytosis and slight increase in the globulins. The diagnosis of uveoparotid fever was verified by biopsy. The authors conclude that paralysis of the facial nerve and neurologic complications of the uveoparotid fever are caused by selective localization of the unknown virus of the disease in the nerves.

J. A. M. A.

REDUCTION OF INTRACRANIAL PRESSURE AFTER OPERATION ON THE BRAIN: PATHOPHYSIOLOGY OF THE CEREBROSPINAL FLUID SYSTEM. H. SPROCKHOFF, Nervenarzt **13**:34 (Aug. 15) 1940.

Sprockhoff points out that in some patients who have undergone surgical operation on the brain the formation of cerebrospinal fluid does not keep pace with the resorption and the result is deficiency and hypotension of the fluid. He lists 11 cases in which there was such postoperative hypotension. With the exception of 2 who had undergone removal of the squama occipitalis, all the patients had a supratentorial defect of the cranium. The patients have headache and are restless and irritable before the hypotensive state develops. The sensorium becomes dulled; slight rigidity of the neck, fatigue, lassitude and nausea develop. There are usually mild hyperthermia and hyperpnea, but the blood pressure and the pulse remain normal. Pallor is occasionally seen. If there is a cranial defect, retraction is noticeable. The pupils become rigid, and reflexes are abolished. Respiration becomes snoring and approaches the Cheyne-Stokes type. This comatose condition may also develop without the prodromal signs. The hypotensive condition does not always lead to complete coma. Differentiation from increased intracranial pressure (brain swelling, arachnoiditis) may be difficult, particularly if there is no cranial defect. The proof that the clinical symptoms described are produced by hypotension in the fluid space is furnished by the fact that intraspinal administration of physiologic solution of sodium chloride promptly counteracts the acute symptoms. If too much fluid is introduced, the skin over the cranial defect will bulge and the undesirable tension may have to be counteracted by another puncture. On the other hand, the retraction in the defect may recur after the filling, so that intraspinal injection has to be repeated. This instability shows that the lack of fluid is not the only cause but that there is also a disturbance in the dynamic equilibrium between formation and absorption of the cerebrospinal fluid. For this reason filling of the

fluid space is not sufficient. As few punctures as possible should be made, because every puncture that is not required to counteract acute hypotension or excess pressure retards the regulation. It is necessary to aid the organism in maintaining normal pressure. Fluid should be given in generous quantities—by mouth in the mild form and by intravenous infusion of solutions of sodium chloride or dextrose in the severe form. The author supported the oral administration of fluid with caffeine in order to increase the blood perfusion of the choroid plexus and thereby stimulate the production of the cerebrospinal fluid. Since erect posture promotes absorption of the cerebrospinal fluid and favors decrease in pressure, this posture should be avoided in cases of hypotension, contrary to the general rule in postoperative treatment. Patients with hypotensive conditions complain of headaches which do not differ from those caused by increased intracranial pressure except that they cannot be improved by the withdrawal of spinal fluid but require intraspinal administration of fluid. The prolonged headaches following lumbar puncture complained of by psychopathic persons or by those with a weak sympathetic nervous system are probably of the hypotensive type. Two of the author's patients had chronic hypotensive symptoms and suffered for years with severe headaches. Both had considerable defects in the cranium, and, having noticed that greater severity of headaches was accompanied by greater retraction, they requested plastic repair, after which they were free from complaints. Reduced secretion is the decisive factor, and this in turn must be due to impairment of the plexus. Various causes, such as senile involution, diffuse atrophy of the brain, prolonged existence of internal hydrocephalus, reduced blood pressure and general exsiccation, may be responsible. The author points out that some employ an exsiccating preoperative treatment in order to avoid postoperative swelling of the brain. This preoperative exsiccation proved its value. The author does not reject the method but emphasizes that it should be used with discrimination, for if it is employed in all cases postoperative hypotension will be more frequent. It should not be employed in cases in which the previous history or the clinical aspects indicate a tendency to hypotension.

J. A. M. A.

METASTATIC TUMORS OF THE BRAIN. M. MINKOWSKI, Schweiz. Arch. f. Neurol. u. Psychiat. **46**:41, 1941.

Minkowski reviews the important contributions concerning metastatic tumor of the brain which have been published since 1900 and reports 17 cases collected from his own experience and that of his colleagues. Metastatic tumor of the brain itself was observed in 13 cases; in 4 of these the primary tumor was a bronchiogenic carcinoma and in 3 others a carcinoma of the breast. There was 1 case of melanosarcoma of the skin with widespread metastases, and in the remaining 5 cases of metastasis within the brain substance the primary growth was a carcinoma of each of the following organs: the cardiac end of the stomach, the head of the pancreas, the rectum, the uterus and the thyroid gland. The intracranial metastasis apparently had its origin in the dura in a fifth case of bronchiogenic carcinoma. In a case of Ewing's sarcoma of the pelvis and in 1 of carcinoma of the prostate gland there were widespread metastases to bone, including multiple metastases of the skull which had invaded the cranial cavity and involved several cranial nerves. Sarcomatosis of the basilar meninges without invasion of the cerebral substance was observed in a case of sarcoma of the upper jaw. This was the only case of the series in which it appeared at all likely that the cranial cavity had been invaded by either the lymphatic or the perineural route.

Multiple cerebral metastases were noted in 3 cases of bronchiogenic carcinoma, in 2 cases of carcinoma of the breast and in the 1 case of melanosarcoma of the skin. In the case of carcinoma of the pancreas the choroid plexus of both lateral ventricles and of the third ventricle were diffusely infiltrated, apparently by direct extension from a large metastasis in the right parietal lobe. A small nodular metastasis and two of microscopic size were observed in the cortex of the opposite

hemisphere. A solitary metastasis was noted in the cerebral white matter in 1 of the cases of bronchiogenic carcinoma and in the case of carcinoma of the thyroid gland. The right half of the cerebellum was the site of a large solitary metastasis in 1 case of carcinoma of the breast and in the single cases of carcinoma of the rectum and carcinoma of the uterus. In 1 case of bronchiogenic carcinoma the cerebellum was compressed by a solitary metastasis apparently arising from the dura. The brain was not examined post mortem in the case of carcinoma of the stomach, the metastatic character of the cerebral tumor being confirmed by microscopic examination of tissue removed surgically. The author's experience and that of a few others would indicate that, contrary to the general belief, multiple metastatic tumors of the brain are not much more frequent than a single metastatic tumor.

Because of the interposition of two capillary filters, one in the liver and the other in the lungs, cerebral metastasis seldom occurs in cases of primory tumor of the gastrointestinal tract. Several cases each of carcinoma of the stomach, carcinoma of the pancreas and carcinoma of the colon and rectum in which intracranial metastasis was observed have nevertheless been reported. Cerebral metastasis is likewise relatively infrequent in cases of carcinoma of either the uterus or the thyroid gland. Metastases were demonstrated in the liver but not in the lungs in the author's case of carcinoma of the pancreas. The liver and lungs were not examined in the case of carcinoma of the stomach or of carcinoma of the rectum. The lungs were examined in 6 of the 9 cases in which the primary tumor lay in a part receiving its blood supply from the systemic circulation, but in only 1 case were pulmonary metastases found. A number of cases of metastatic carcinoma of the brain have been reported in which pulmonary involvement could not be demonstrated even on microscopic examination. It has been suggested that small pulmonary metastases may be encapsulated and later destroyed. Minkowski expresses the view that malignant cells may pass directly from the lesser to the greater circulation by way of the pulmonary capillaries. In none of his cases of carcinoma of the breast was there evidence to indicate that the cranial cavity had been invaded by retrograde transport along the cervical lymphatics.

The microscopic structure of the cerebral metastases in Minkowski's cases was similar to that of the primary growth. Though in general, and in keeping with the experiences of other observers, mesodermal reaction was slight, there was a well developed connective tissue stroma in a few instances. Both the glial and the mesodermal reaction were more evident at the periphery of the tumor than in its interior, but in only a few cases was there a definite zone of demarcation. General changes within the brain were similar to those observed in cases of primary tumor and could be accounted for on the basis of increased intracranial pressure, stasis of the blood and cerebrospinal fluid and cerebral edema. In view of the degenerative changes frequently occurring in malignant growths, however, the belief is expressed that there may be an added toxic factor in cases of metastatic tumor. Diffuse metastatic infiltration of the meninges is seldom associated with the presence of gross metastases in the parenchyma of the central nervous system.

The frequent clinical latency of the primary growth in cases of metastatic tumor of the brain is emphasized. In the case of carcinoma of the pancreas symptoms of cerebral involvement antedated the appearance of icterus by two weeks. Results of roentgenologic study of the chest were negative in 1 case of bronchiogenic carcinoma, although emaciation and the presence of an enlarged cervical lymph node were observed. Signs and symptoms of gastric involvement were overshadowed by those of the cerebral tumor in the case of carcinoma of the stomach. The first symptoms in the case of carcinoma of the prostate gland were indicative of a lesion in the posterior cranial fossa. Although symptoms of pleural metastasis were noted later, both the primary growth and the metastases in the long bones remained clinically silent.

The first symptoms of cerebral involvement in the majority of cases reported here were more or less general, consisting of headache, dizziness, nausea, vomiting and general weakness. In a number of cases mental changes, such as depression, irritability, lability of affect and disturbances of the sensorium, predominated at the time of onset. In only 3 cases were the initial symptoms focal in character. Occasionally signs of focal involvement came on abruptly after a short period of mild general symptoms. The course, in general, was rapidly progressive, although the mental symptoms in particular showed some tendency to temporary remission. The average duration was two and seven-tenths months, the longest period of survival being five months.

Hemiparesis, with characteristic changes in the reflexes, was noted in 8 cases, in 4 of which there was associated hemihypesthesia. Amnesic aphasia was succeeded by severe aphasia of the sensory type in 4 cases. In 2 cases of the latter group, including 1 of multiple tumors in both hemispheres and the corpus callosum, there was also severe apraxia. Characteristic local signs were more or less pronounced in the 4 cases in which the cerebellum was involved.

Taken by itself, the neurologic picture does not in general permit of a differentiation of secondary and primary tumors of the brain. Only rapid progression associated with usually pronounced mental symptoms and the sudden appearance of more or less unrelated neurologic signs would lend a certain degree of probability to the diagnosis of metastatic tumor. Most essential for the diagnosis of metastatic tumor of the brain, therefore, is the discovery of a malignant tumor lying ouside the nervous system. Such tumors are always to be searched for in persons of middle age or older who present symptoms of an intracranial neoplasm. In addition to a complete physical examination, roentgenologic study of the lungs and tests for the presence of blood in the urine and feces are especially indicated. Determination of the sedimentation rate of the red blood cells is also helpful, since it is usually much higher in cases of metastatic tumor of the brain than in cases of primary cerebral neoplasm.

Minkowski expresses the view that since metastatic tumor of the brain is by no means always multiple, an attempt at surgical removal with a view to prolonging life may be justifiable at times. Otherwise, the only treatment indicated consists in relief of headache by means of analgesic drugs and intravenous injections of hypertonic solutions.

DANIELS, Denver.

AUJESKY'S DISEASE IN TURKEY IN ANIMALS AND IN MAN. I. SCHÜKRÜ-AKSEL and ZEKAI TUNCMAN, Ztschr. f. d. ges. Neurol. u. Psychiat. **169**:598 (May) 1940.

In 1902 Aujesky described a disease resembling rabies in animals. Only 1 case of infection by the Aujesky virus in a human being is on record. The authors examined 4 animals with this disease in the Antirabies Institute at Istanbul, Turkey. Most of them were sent to the laboratory because of suspected rabies, and all showed diffuse meningoencephalitis. The gray matter was particularly involved, especially the cerebral cortex and the periventricular areas. In the cases of spontaneous infection the infiltrating cells were predominantly of the plasma type, though in some cases of the very acute form many leukocytes were seen free in the tissues. The choroid plexus was involved in all cases. Negri bodies were not found. The substantia nigra, pons and bulb were not involved by the disease process, in striking contrast to the usual occurrence in rabies.

A characteristic sign in animals to which the disease was transmitted by inoculation was the peculiar attitude which they all assumed. They looked as though they were stuffed (*forme empaillée*). Wherever the virus was injected subcutaneously there was marked pruritis. In the authors' experiments saliva was shown not to be infectious. In 1 instance the infection was transmitted from one animal to another in the laboratory by a bite. Animals with the disease acquire immunity. Injections of antirabies serum do not protect against Aujesky's disease. The virus which was studied in the author's laboratory had a very short

incubation period. Inoculated animals usually died within eighteen hours. Infection can be transmitted through the gastrointestinal tract. It is generalized, involving all organs, but is definitely neurotropic.

The authors report 2 cases of the disease in man. Both were laboratory workers. A male laboratory assistant injured his hand during an autopsy on an animal with Aujesky's disease. He had persistent pruritis and reddening of the skin for twenty-four hours. A woman working in the same laboratory cut a finger with glass. On the same day she complained of being exhausted and in the next few days had pruritis in the injured hand. This pruritis extended up the arm to the shoulder. The white blood cell count was 5,625, with 60 per cent polymorphonuclear leukocytes. There was a slight amount of albumin and sugar in the urine. A rabbit inoculated with the blood serum of this woman died in eighteen hours with Aujesky's disease. The pruritis lasted forty-eight hours. After the itching cleared up she complained of headache and weakness, had erythematous patches on the lower limbs and aphthous lesions in the mouth. She was well in three days.

SAVITSKY, New York.

Vegetative and Endocrine Systems

PUBERTAS PRAECOX DUE TO OVARIAN TUMORS. C. B. LULL, Am. J. Obst. & Gynec. **41**:445 (March) 1941.

Lull cites 2 cases of ovarian tumor associated with precocious puberty. He considered 1 of the tumors to be a typical granulosa cell tumor and the other a simple follicular cyst of the ovary. The fact that the second patient responded to operative procedure and returned to normal infantile type leads him to believe that surgical intervention is indicated in cases of such a tumor, even though it is not of the granulosa cell type. Functioning tumors of the ovary today represent such broad possibilities as to be of interest to the medical profession in general. From an endocrinologic point of view these tumors furnish definite evidence of hormone production and its clinical effects. To the embryologist the various phases of cellular differentiation are of especial interest. The general interest in the study of these tumors has been stimulated to such a degree that today the probability of a positive diagnosis and a more favorable prognosis in the majority of cases is increased.

J. A. M. A.

PRECOCIOUS PUBERTY AND TUMORS OF THE HYPOTHALAMUS. LAWRENCE M. WEINBERGER and FRANCIS C. GRANT, Arch. Int. Med. **67**:762 (April) 1941.

A careful review of the literature on the relation between tumors of the pineal body and precocious puberty reveals a mass of contradictory statements. In 1923 Krabbe reviewed 200 publications and stated: "We must point out that the hypothesis that the secretion of the pineal gland plays a role in the development of puberty is to date completely without significant evidence. One has often the impression that the authors' desire to consider the organ incretory in function is greater than their critical judgment regarding their published researches." Weinberger and Grant feel that Krabbe's criticism is still applicable. The secretory nature of the pineal gland is still unproved, though some authors cling to the belief that it elaborates a substance affecting sexual development.

In recent years attention has been directed to the role which hypothalamic disturbance plays in relation to precocious puberty. In an analysis of all the collected cases of pubertas praecox associated with pineal tumor, it was found that in 70 per cent there were symptoms or signs referable to hypothalamic involvement. The authors believe that precocious puberty is merely a rare variant of sexual disturbances of hypothalamic origin, the reverse of the genital atrophies and sexual infantilism so well known to occur with disease in this region. Fifteen cases have been reported in which tumor of the hypothalamus and third ventricle was present and in which the pineal body was not affected.

The case of a 7 year 11 month old boy was reported in detail. His is the second case of precocious puberty occurring with a tumor of the central nervous system in which there was an opportunity to make complete endocrinologic studies with modern technics. Of interest was the fact that the patient survived an operation in which a large mass of tumor was removed.

On the basis of their studies Weinberger and Grant offer the following explanation of the genesis of precocious puberty: Lesions of the posterior portion of the hypothalamus interrupt nerve pathways or interfere with mechanisms which normally inhibit and control the production and release of gonadotropic substances from the anterior lobe of the hypophysis. The excessive liberation of these pituitary substances stimulates the ovaries in the female or the interstitial cells of the testes in the male to overproduction of their specific principles, the estrogenic and androgenic substances, which are responsible for the development of the secondary sexual characteristics. The proof of the hyperactivity of the anterior lobe of the hypophysis is found indirectly in the presence of abnormally large amounts of estrogenic and androgenic substances in the urine of patients with precocious puberty.

In summary, it is stated that tumors or other lesions of the hypothalamus may be associated with precocious puberty even though the pineal gland is unaffected. Because of the anatomic positions of the pineal gland, tumors arising from it or in its neighborhood almost invariably destroy or compress the posterior part of the hypothalamus. There is no unequivocal evidence that the pineal body has a secretion which affects sexual development, and it is submitted that precocious puberty is a pure hypothalamic syndrome. There is no experimental evidence that lesions placed in the posterior part of the hypothalamus will cause precocious puberty, and the authors suggest this line of attack as worthy of investigation.

BECK, Buffalo.

INDUCTION AND COURSE OF PERMANENT DIABETES PRODUCED BY ANTERIOR PITUITARY EXTRACT. F. C. DOHAN, C. A. FISH and F. D. W. LUKENS, Endocrinology **28**:341 (March) 1941.

The authors report detailed studies on the induction and course of permanent diabetes in 10 dogs. In 2 dogs diabetes was not produced by injection of the anterior pituitary extract. After partial pancreatectomy, however, permanent diabetes was produced after small amounts of the pituitary extract had been given. It was noted that in dogs adequately treated with insulin the rate of progress of the diabetes was inhibited after injections of the anterior pituitary extract had been stopped. Feeding of liver or pancreas and administration of zinc oxide had no effect on the course of the diabetes. In 1 dog a cataract developed.

Other observations support the concept that the diabetes which continues after withdrawal of anterior pituitary extract is due primarily to loss of function of the islands of Langerhans. There is conspicuous atrophy of the islands, and of the cells remaining the alpha type are in preponderance. In the most severely diabetic dogs, the response to insulin, the fasting urinary dextrose and nitrogen excretion and the amount of glycogen in the liver were similar to those in totally depancreatized dogs.

PALMER, Philadelphia.

INHIBITION AND STIMULATION OF TESTES IN RATS TREATED WITH TESTOSTERONE PROPIONATE. H. SHAY, J. GERSHON-COHEN, K. E. PASCHKIS and S. S. FELS, Endocrinology **28**:485 (March) 1941.

The authors found that although treatment of young rats with 3 mg. of testosterone propionate per week leads to decrease in the weight of the testes, inhibition of maturation of spermatozoa and damage to the interstitial tissue, similar treatment, but with doses of 30 mg. per week, results in increase in the weight of the testes and stimulation of spermatogenesis. This is true in animals so treated from the first to the thirtieth or from the thirtieth to the sixtieth day of life. In animals

treated with the large doses from the first to the sixtieth day of life the weight of the testes is decreased and spermatogenesis is inhibited, but the latter result is less marked than in rats of the same age treated with 3 mg. per week. In all instances the interstitial tissue shows signs of damage. As a tentative explanation of these and other observations, the authors assert that testosterone propionate stimulates the testes directly and at the same time exerts an inhibitory influence on the testes through inhibition of the gonadotropic hormone of the pituitary. During the first month of life the inhibitory influence has less effect on the outcome when large doses are used, whereas later the effect is intermediate between direct stimulation and indirect inhibition. Much larger doses are necessary to produce the direct stimulation of the testes; that is, the pituitary gland is more sensitive to the action of testosterone than the testes.

PALMER, Philadelphia.

CUTIS VERTICIS GYRATA ACCOMPANYING ACROMEGALY. HERMANN PITZ, Ztschr. f. d. ges. Neurol. u. Psychiat. **168**:269 (Jan.) 1940.

This unusual condition was described in a case of acromegaly for the first time by Parkes-Weber in 1928. The skin of the scalp becomes inordinately thickened and folded, presenting the appearance of the gyri of the brain. As a result of the hypertrophy the skin becomes wrinkled and furrowed. Pitz reports 2 additional cases. In both there was typical acromegaly. The duration of the disease was nine years in 1 case and nineteen years in the other. Only 1 of the patients had a chiasmal syndrome, and 1 had the hyperglycemia often seen in association with acromegaly. The patients were both men, 46 and 45 years old. No other cutaneous changes were noted in the scalp. The skin of the scalp was freely movable over the underlying skull.

SAVITSKY, New York.

Treatment, Neurosurgery

PROLONGED COMA IN INSULIN THERAPY OF PSYCHOSES. HERVEY CLECKLEY and C. M. TEMPLETON, Am. J. Psychiat. **97**:844 (Jan.) 1941.

Cleckley and Templeton report 6 cases of prolonged insulin coma, the duration of the coma varying from three and a half hours to eight days. In 2 cases (duration of coma eight days and twenty-nine hours respectively) the termination was fatal. The cause of the prolonged coma could not be determined. Therapy with members of the vitamin B group, either prophylactic or given during the coma, yielded no results. In 1 case potassium chloride brought about cessation of convulsions, and the authors recommend its use in cases of prolonged insulin coma.

FORSTER, Boston.

THE EFFECTS OF TESTOSTERONE PROPIONATE IN IMPOTENCE. HUGH T. CARMICHAEL, WILLIAM J. NOONAN and ALLAN T. KENYON, Am. J. Psychiat. **97**:919 (Jan.) 1941.

Carmichael, Noonan and Kenyon studied the effects of testosterone propionate on 18 men who were sexually impotent without organic cause. Psychotherapy was carefully avoided during the experiment. The ages ranged from 21 to 61 years. Six of the subjects were single. Testosterone propionate was given intramuscularly in 25 mg. doses three or more times a week, the total number of injections per patient varying from ten to fifty-one. Control injections of sesame oil were also used. During the treatment 7 of the 18 patients received satisfactory relief; this relief persisted after therapy in 6 cases. The authors concluded that the successful effects were probably due to psychologic factors.

FORSTER, Boston.

COMBINED ARTIFICIAL FEVER, CHEMOTHERAPY AND VACCINOTHERAPY FOR NEUROSYPHILIS. A. MARIN, Canad. M. A. J. **44**:161 (Feb.) 1941.

From October 1937 to January 1940 Marin treated 220 patients suffering from neurosyphilis, chorea, multiple sclerosis, gonorrhea and other diseases with a combination of vaccine, chemotherapy and hyperpyrexia. His treatment consists of an injection at 7 a. m. (for example, on Monday) of tryparsamide followed immediately by a session of five hours of artificial fever at 105 F. On Wednesday and Friday the patient is given an injection of fever-producing vaccine, such as pyrifer (a nonspecific protein mixture prepared with extracts of fever-producing bacteria [colon bacilli] of nonpathogenic stocks), and of a bismuth compound. Vaccines produce an average temperature of 104 F. This procedure is repeated for ten weeks, after which the patient is treated at the outpatient clinic with pentavalent arsenic or neoarsphenamine and bismuth compounds. The 220 patients received 1,318 treatments of about five hours each, with a total of 7,568 hours. There was 1 death. Among the group there were 137 patients with neurosyphilis, and 89 of these had fifty hours of artificial fever combined with administration of vaccines and chemotherapy. Far from being debilitating, the combined therapy produced general improvement. The majority of the working people with asymptomatic syphilis could carry on their occupation. Restlessness, insomnia and headaches decreased or disappeared during the hyperpyrexia or shortly afterward. The weight of many emaciated patients increased. In patients with tabes, lightning pains and vomiting decreased or disappeared. There was improvement in muscular strength or in gait. In patients with dementia paralytica the remissions (complete or incomplete) usually occurred between the fifth and the tenth session of pyretotherapy. In 3 patients there was a "flare-up" of the delirium by the end of the fiftieth hour; 2 of these had complete remissions during the next two months. The percentage of full remissions (return to former occupation) among the patients with dementia paralytica was 54. Of the 89 patients, 39 are eliminated from serologic study, 18 have been under treatment for less than six months and 21 discontinued treatment at the outpatient clinic, followed it irregularly or refused to have a third lumbar puncture (one before and one after the combined treatment and one after adequate outpatient chemotherapy). The 50 patients were under treatment for from six to eighteen months. Although eighteen months of treatment is not long in cases of neurosyphilis, and six months is almost insignificant, the patients are considered as one group. Before treatment there was a strongly positive fluid in 68 per cent of cases, as compared with 26 per cent after treatment. There are now negative fluids in 22 per cent of cases, whereas there was none before treatment was started. The weakly positive and doubtful fluids, which at the onset were found in 16 per cent of cases are now found in 30 per cent. It is logical to expect that many of these will soon increase the proportion of the negative group. The 11 patients whose spinal fluid became negative did not all present the same degree of abnormality at the onset, nor did they respond evenly to the treatment.

J. A. M. A.

DILANTIN SODIUM THERAPY IN EPILEPTIFORM SEIZURES OF CHILDREN. E. C. LOWRY, Journal-Lancet **61**:178 (May) 1941.

Lowry used dilantin sodium in the treatment of epileptiform seizures of 34 children from 5 months to 16 years of age. The children were placed on a water restriction diet (900 cc. a day). The dosage of dilantin ranged from 0.2 to 0.4 Gm. daily, depending on the age and the tolerance of the child. Twenty-four had grand mal attacks, 2 had petit mal and 8 had seizures of both types. Two thirds of the children were treated for one year or more and one fifth for two years or more. The following results were obtained: Three children had complete cessation of seizures; 19 were improved (only 5 moderately), and 12 were not benefited. In many the attacks became milder. The 65 per cent of favorable results is comparable to the experience of most workers, but some have reported a higher

percentage of complete remissions. In all but 1 (whose seizures ceased) of the 23 children who received dilantin sodium continuously for a year or more the benefit was maintained throughout the period of observation without any increase in dosage, indicating that in general children do not acquire a tolerance for the drug. Most of the patients felt no ill effect from the medication. Patients with the most frequent attacks were most benefited. Phenobarbital and dilantin sodium were given to patients whose response to the latter medicament was unsatisfactory, and enough of these children improved to suggest that the combination is worth trying when other methods have failed.

J. A. M. A.

NEURAL MYATROPHY AND VITAMIN E. W. DE GUTIÉRREZ-MAHONEY, South. M. J. **34**:389 (April) 1941.

Gutiérrez-Mahoney considers types of neural myatrophy which from their first recognition have been called progressive muscular atrophy. Depending on the distribution of the wasting and the presence or absence of spasticity, they have been variously named bulbar palsy, pseudobulbar palsy, a combination of the two, atrophy of the muscles, amyotrophic lateral sclerosis or a combination of all these forms. They are one and the same disorder, affecting mainly the motor neurons ("motor neuron disease"). De Gutiérrez-Mahoney cites his experimental and clinical observations, begun in June 1938. Because of the clinical and microscopic changes which followed deficiency of vitamin E in the diet of rats and could be prevented if vitamin E was added to these diets, the author concluded, in spite of some dissimilarity between the clinical and pathologic pictures of the rats and those of patients suffering with progressive muscular atrophy, that the administration of vitamin E to such patients might be beneficial. During the two years he has seen and treated 9 patients with the type of neural myatrophy which from experimental and clinical studies seemed to come under the class due to E deficiency. Three patients showed no improvement after treatment with a defatted concentrate of vitamin E from wheat germ oil. They had the advanced stage of the disease and were suffering from bulbar palsies as well as from peripheral wasting. The other 6 improved; 3 of those had wasting with weakness of the hand muscles, 1 had wasting about the neck and shoulder girdle and the other 2 had little wasting but definite spasticity. Two of the patients with wasting of the hand muscles and 1 with spasticity of all the limbs discontinued taking the vitamin concentrate after having had improvement, and their conditions regressed to the previous disability. They resumed taking the material, and improvement recurred. One of these patients lapsed in treatment a second time, and his condition became worse but again improved when he took the wheat germ oil concentrate. With the improvement in the localized weakness a marked increase in the general strength and vigor of these patients occurred. In 2 patients there was filling in of the previously wasted hand muscles. One man continued to have fasciculation of his muscles, though to a diminished degree, while improvement during the two years of observation progressed from inability to walk without a stick to being able to run well and to return to work. Improvement usually appeared within a fortnight to a month after starting to take vitamin E. Treatment of the dystrophies in which the nervous system was not intact did not cause any improvement in the patient's condition. These control observations included those in patients with the muscular dystrophies, myasthenia gravis or thyrotoxic myatrophy. Thus the author feels that some neural myatrophies due to a deficiency of vitamin E can be corrected if they are identified early and vitamin E is supplied before the condition has progressed to the stage where too many of the nerve cells have been irreversibly damaged. He suggests the possibility that infantile cerebral palsy results from vitamin E deficiency in the mother before birth and during lactation. In tracing the probable cause of the trouble one is often unable to attribute it to any of the suggested possibilities, and it does not seem unreasonable to him to assume that the palsy is due to the deficiency. To demonstrate this conclusively, administration of vitamin E to a large and carefully observed series of pregnant women

would be required, and this would have to be controlled by a series not given supplementary vitamin E, with subsequent calculation of the incidence of infantile cerebral palsy in the offspring of each group. Vitamin E might also be administered to newborn children as soon as infantile cerebral palsy is recognized, with the hope of preventing further disability and possibly of correcting the condition itself.

J. A. M. A.

DESOXICORTICOSTERONE ACETATE IN DYSTROPHY OF INFANTS. F. J. MENCHACA and N. Albarracin, Arch. argent. de pediat. **15**:15 (Jan.) 1941.

Menchaca and Albarracin administered desoxicorticosterone acetate in conjunction with proper hygienic and dietetic therapy in 7 cases of dystrophy in infants in the first six months of life. The drug was administered in daily injections of from 1 to 1.5 mg. until from fourteen to twenty-five injections had been given for each series. The treatment consisted of two series of injections with a fifteen day interval. Satisfactory results were obtained in all but 1 case, in which dystrophy was complicated by a pulmonary infection. The drug seems to have an especially favorable effect on the appetite and general condition of the patient, causing gain in weight.

J. A. M. A.

ELECTRIC SHOCK THERAPY. H. CERLETTI, Wien. med. Wchnschr. **90**:1000 (Dec. 28) 1940.

Cerletti reviews the status of the electric shock therapy of mental disorders. Experiments with different species of animals (dogs, cats, hogs) induced him to try the procedure on human subjects. He learned that it is much less dangerous to pass the electric current through the brain than through the trunk, because in the latter passage the heart is affected. His aim was to find a substitute for the metrazol shock therapy of schizophrenia. Convulsions are elicited with a current of from 70 to 110 volts (300 to 600 milliamperes). The majority of investigators agree that this voltage is best, but some have employed voltages up to 150. The author passes the current for one tenth of a second, though some investigators pass it for longer periods. The variations in voltage and time indicate that the method has wide limits of tolerance. The number of convulsions necessary to obtain a therapeutic result varies greatly, depending on the type of disease and the individual patient. In cases of melancholia and manic-depressive psychosis complete recovery has been obtained with four to six applications. The treatment must not be terminated too early. At the author's clinic the electric shock treatment is usually applied two or three times a week; in other clinics it is given more frequently. Comparisons with the insulin shock therapy revealed that the electric shock therapy is preferable in all cases of mental disturbances accompanied by depression, especially in those with psychomotor inhibition or retardation. The author employs electric shock in the majority of cases of schizophrenia. Insulin shock is preferable when the patient is in a state of psychomotor excitation or is emaciated. In cases of schizophrenia and of manic-depressive psychosis recurrences are likely and treatment should be repeated as soon as signs of relapse appear. Braunmühl suggested that in the treatment of mental disorders of a periodic nature the electric shock therapy be repeated from time to time in order to prevent recurrences.

J. A. M. A.

Society Transactions

PHILADELPHIA PSYCHIATRIC SOCIETY

LAUREN H. SMITH, M.D., *President, in the Chair*

Regular Meeting, Oct. 17, 1941

Schizophrenia in a Five Year Old Child: Report of a Case. DR. GERALD H. J. PEARSON.

This case is reported for two reasons: (1) because of its rarity and (2) because of the unusual importance as a causative factor attached to the patient's upbringing.

The patient was a tall, thin, active Negro girl, the daughter of a physician and a school teacher. Early infancy was normal, and the patient was breast fed for several months. Before her birth the physician father laid down an absolute rule that the child should not be spoiled, that she should not be touched, looked at or spoken to except when her routine care demanded it. This rule was strictly adhered to. At 3 years of age the child presented behavior peculiarities that were quite noticeable. She had frequent uncalled-for temper tantrums and displayed much anxiety when her usual routine was disturbed in the least. She showed no emotional relationship whatever to any other person. When first examined at 4 years of age, she was very restless and showed no sustained interest in anything. She looked at the physician, began to cry, had a temper tantrum and then began to dance about in a most unusual way. Most of her time was spent in seemingly endless and aimless running. Her speech was difficult to understand because she used only irrelevant fragments of sentences and often merely talked to herself. Rapport was never established. When the mother began to play the piano, the patient immediately sat down in a little chair and her facial expression changed completely, as if she were in an entirely different world. Her interest in the music was intense. Later she herself played simple tunes, displaying considerable aptitude for one of her years. One tune she played entirely on the black keys.

The Vineland social maturity scale revealed a social age of 3 years 8 months, 7 months below her chronologic age. Activities involving self help, communication and socialization were more poorly performed than those of occupation and locomotion. Her speech was underdeveloped and her pronunciation poor. Memory was excellent, and she was most observant. In general her intelligence was believed to be normal.

Six months later the child had changed little. She ignored the physician, and her attention could not be gained in any way. She wandered aimlessly about the room, usually on her tiptoes, except when she or her mother played the piano, when she listened as if enraptured.

A few months ago she was admitted to the children's department of the Allentown State Hospital.

DISCUSSION

DR. MAX ROSSMAN, Allentown, Pa.: I have had occasion to study this patient at the Allentown State Hospital. There is something about the contact that this child makes with other people and the activity she indulges in which gives the impression that she is completely detached from her environment. She takes things very passively. This attitude may be described as a narcissistic relation with reality—she is quite satisfied as long as she gets what she wants, but she is not willing to give anything in return. Since her first week at the hospital she has made a fairly good adjustment.

DR. LAUREN H. SMITH: I was fortunate in being able to see this child. Having seen a great many encephalitic children, I at first glance wondered if

this behavior was not one of the postencephalitic types, but it did not take long in examination to give the impression that the condition was entirely different from any postencephalitic disease.

I believe schizophrenia is uncommon in childhood. Perhaps schizophrenic behavior is common, but schizophrenia, as it exists in this child, is not usual. Schizophrenia is usually progressive, and if it occurs in childhood, the patient is not likely to make a normal adjustment. It would be interesting to follow her progress through some years.

DR. A. M. ORNSTEEN: I did not hear Dr. Pearson say anything about the neurologic examination. I assume that an organic cerebral defect was excluded. He said that she always walks on her toes. Is this caused by spasticity of the lower limbs? If not, is it then a behavior characteristic? Organic cerebral defects in early childhood are quite common, but the diagnosis in this case is strikingly unfamiliar to me, and I heard Dr. Smith say the same thing. I suppose Dr. Pearson means that the patient has dementia praecox, or a schizophrenic behavior disorder. I should like to know whether he considers that this child was normal until the onset of her behavior change or whether there may have been an acute infection in infancy, such as cerebral fever, which was not diagnosed.

DR. GERALD H. J. PEARSON: My examination of this child showed no symptoms of an organic cerebral disturbance. Her legs were not spastic. She walked on her toes only when she had one of her tantrums. Her reflexes were normal. I do not think she has a cerebral defect. I believe that her intelligence is good. Certainly a child who can learn poetry and a good many other things without being taught does not have much cerebral impairment. Her illness began at the age of 18 months. There is no history of any previous infection. I feel that the main difficulty has been that she has been very much neglected since she was 18 months of age, with only the minimum of care, and her only relation has been with routines. If she expected her mother home about 5 o'clock, she would run back and forth to the door and cry until she appeared, though instead of hugging and kissing her mother, as would be expected, she paid no attention to her. If she had her bath before dinner, she had anxiety and wanted to have it again after dinner. There is one point I neglected to mention. I told the mother that she should go out of her way to give the child more attention, which she did for over a year, and the child started to respond.

Schizophrenia in childhood is not common. My colleagues and I see 1 or 2 cases a year in which the condition is undoubtedly schizophrenia.

Adjuvant Treatment of Toxic States: A Preliminary Report. DR. EDWARD A. STRECKER and DR. THURSTON D. RIVERS.

This is a presentation of an attempt to treat toxic states, particularly alcoholic intoxication, by physiologic means. Sedation, which has formed the basis for the treatment of toxic states, may in itself become a toxic agent. Therefore a therapy based on physiologic factors offers great advantages. A short review of the literature offers a rationale for this treatment.

One hundred cubic centimeters of a 50 per cent solution of dextrose, 30 units of insulin and 100 mg. of thiamine hydrochloride were injected intravenously and the medication repeated in three hours if necessary. This combination would seem to increase the carbohydrates available to the liver and the rate at which products are detoxified by the liver.

Other clinicians have used these agents for the elimination of alcohol but have never administered them intravenously in combination. The cases of 133 patients treated under varying conditions are presented.

Results seem to warrant the conclusion that this treatment offers a more physiologic approach to an important medicopsychiatric problem. It can with dispatch handle an acute problem from the standpoint of physical control and elimination of unpleasant symptoms, at an economic saving to the patient and the hospital.

DISCUSSION

DR. HOWARD P. ROME: In the service of Dr. Kenneth E. Appel at the Institute of the Pennsylvania Hospital, my associates and I have had the opportunity to employ the treatment Dr. Rivers has suggested for somewhat over a year. Our results are of the same order as those he reports. A typical instance is that of a patient seen this afternoon, with acute alcoholic hallucinosis. He had been drinking for the past seven days, had had nothing to eat for the past five days and for the last three days had been vomiting blood. A solution of insulin, dextrose and thiamine hydrochloride was given as described, and in an hour there was a perceptible alteration in the clinical picture. Psychomotor hyperactivity had disappeared. There were no hallucinations; affect was appropriate, and he was accessible to a degree which was not permissible previously. He ate a full dinner, the first meal in five days. After this, without additional sedation, he fell asleep. We anticipate continuing the medical management as already indicated. Not all our results are as satisfactory as this, but on the whole we can corroborate the statistics presented this evening.

DR. W. COLE DAVIS, Atlantic City, N. J.: Dr. Rivers described this treatment to me some time ago. Last week I was called in consultation to see a patient with delirium tremens and to decide to what hospital he should go. When I saw him he was not so wild as he had been. He was just seeing his brother and a few other persons around the room who were not there; so I suggested keeping him at home and trying Dr. Rivers' treatment. The next day he had no recollection of having seen me before. His condition had cleared up entirely; he had a fine appetite and was feeling well.

DR. KENNETH E. APPEL: Dr. Rivers has made a fine presentation of an interesting subject, and I believe it will bring up many questions. I should like to ask him how much of the effect of his treatment is due to the chemical action of the injections and how much to the physiologic or physical effect of the solution injected.

DR. A. M. ORNSTEEN: I should like to ask Dr. Rivers if he can compare the physiologic effects of a hypotonic solution of sodium chloride and those of the insulin-dextrose-thiamine solution. For a while at Bellevue Hospital a hypotonic salt solution was employed routinely. Its use may have been discontinued, but for a while this treatment compared favorably with many others; if it is comparable, how can Dr. Rivers explain and correlate the results of the two treatments?

DR. THURSTON D. RIVERS: Dr. Appel, we have used hypertonic sucrose solution alone in management of toxic states but have observed no dramatic results. Other investigators have used 10 per cent dextrose, 600 cc., given intravenously by the drip method, in conjunction with insulin, given subcutaneously, with good results. It would seem that the hypertonicity of the solution does not account for its action. Whether this is a purely chemical reaction I do not know, and I do not think any one else knows. Other investigators have attempted to find an agent which would reduce the alcohol levels in the blood. Thyroid, given for several days, dinitrophenol and diathermy were the only agents other than the insulin-dextrose solution which were found effective.

I am not familiar with work done by Dr. Bowman with hypotonic salt solution. I do know that Dr. Bowman is one of the authors of a recently published article recommending the use of insulin and dextrose in management of acute alcoholism.

Unity and Continuity of Personality. DR. ARTHUR P. NOYES.

There are many conceptions of personality, any definition proposed being usually constructed in the terms of that discipline in which the formulator is trained to think. Perhaps the psychobiologist may define the personality as that organism of constitutional, affective, ideational and conative capacities and tendencies which characterize the person and largely determine his habitual patterns of behavior.

While its organic background determines the general pattern according to which the personality is fabricated, individual characteristics, nevertheless, are influenced less by the constitutional than by the more dynamic, conative and affective forces. Yet these conative and affective aspects of the personality have also their natural history, their logical continuity, as do phenomena integrated at the structural level. The principle of continuity applies to various manifestations of the personality, healthy or diseased, as well as to other phenomena of nature. To understand his patient the psychiatrist attempts to retrace the thread of the personality development. Inner experiences, external influences, instinctive drives and their frustrations, psychologic needs and stresses of the personality and the mechanisms by which the personality reacts to these demands and strains are biologic facts no less than physiologic states, although they must be studied more in terms of the whole organism.

Approaching this problem from a genetic and dynamic point of view, one must seek to understand the person in terms of his own life history, with his specific emotional problems. With an analytic historical perspective of the personality the psychiatrist brings experiences and events into etiologic relation with its present status, whether that is one of successful adjustment or is characterized by psychopathologic disturbance.

Symptoms are rational but extreme psychobiologic reactions, the exaggeration of processes that have long been operative in the organism—processes, however, which, because they did not adequately meet the emotional and other needs for which they were created, became intensified until finally they came to stand out so strikingly as to be called symptoms, and if disregardful of reality, called psychotic symptoms. They are, therefore, logical sequences of the adaptive mechanisms by means of which the organism has striven to attain its goals. Like more narrowly biologic phenomena, such as fever, inflammation and other morbid processes, many personality characteristics which are conspicuously exaggerated and fixed, as well as most psychoses, are defensive, protective and reparative in purpose. Both such personality characteristics and the psychosis are expressions of the psychobiologic organism's attempt to effect an adjustment to the interplay of psychologic, social and physiologic forces impinging on it, the psychosis often representing a progressive evolution of the personality's measures. When the significance of the patient's personality pattern is ascertained the psychosis is seen to have a logical place in the evolution of that pattern, to be but another instance of the adaptive character of biologic phenomena. The personality is the product of the total forces acting in and on the organism; those expressions of it which are designated as psychoses are therefore likewise the product of these forces.

Personality in Cases of Psychosomatic Disorders. Dr. John M. Flumerfelt and Dr. Baldwin L. Keys.

A series of 100 cases was studied in the wards of a large urban hospital over a period of a year. In each case the patient was seen by a psychiatrist in consultation and was found to have definite psychologic abnormalities. In 31 per cent of the cases clinical and laboratory examination showed evidence of physical disease that appeared to be related to the physical symptoms, but also in these cases psychologic factors appeared to play an important role in precipitating symptoms or in furthering their continuance. In 32 per cent of the cases a positive clinical picture was revealed in the hospital, but in these cases the findings did not appear to be in any way related to the physical symptoms presented. In 18 per cent of the cases the relation between positive clinical findings and the physical symptoms was uncertain. In 19 per cent of the cases thorough study did not reveal any positive clinical signs.

An attempt was made to classify the psychologic disturbances under the current classification for neuroses. Only 7 of the 100 cases fitted clearly and cleanly into any one picture of a neurosis. The bulk of them could be classified only as instances of mixed psychoneuroses. This seems too general to be useful.

Certain personality traits were common to 52 of the 100 cases. The outstanding personality traits were clinging to others, childish reactions to life problems, insecurity and anxiety, and resentment manifested over a long period.

The voluntary physical complaints of the patients and their complaints of psychologic nature were matched with each other. Anxiousness, insomnia and irritability were the complaints of psychologic nature noted most frequently throughout the series. Irritability, feelings of inferiority, and feelings of despondency were found notably more frequent in cases of bronchial asthma than in the series of 100 cases as a whole. None of the patients with bronchial asthma complained of feelings of tension.

In cases of low abdominal pain there were a definite increase in lack of interest and pronounced avoidance of other people as compared with the average incidence for these symptoms in the series.

An attempt to apply current classifications for psychoneuroses to 100 cases of psychosomatic illness has been unsatisfactory. There are peronality traits common to one half of the cases studied. When a patient has physical complaints involving one part of the body or another, differences of character and degree of intensity of the psychologic symptoms are shown in many instances, depending on the part of the body affected by the physical symptoms.

DISCUSSION

DR. JOSEPH C. YASKIN: I should like to ask the essayists to clear up certain matters in their interesting presentation. I received the impression that the 100 cases did not include any in which there was definite somatic disease; yet on the chart are shown cases of definitely established hyperthyroidism and asthma.

In some cases of abdominal pain, headache and other familiar manifestations the symptoms were said to be due to physiologic disturbances, but in this group the "anxiety neurosis" type was excluded. I assume that in this group the symptoms were unaccompanied by anxiety corresponding to the so-called conversion hysteria type.

It would appear that in the majority of cases studied the condition belonged to what was previously designated neurasthenic state and now called anxiety hysteria. I am at a loss to understand why such a condition should be designated as psychosomatic. Headache, abdominal pain, insomnia and most of the other symptoms tabulated are common in anxiety hysteria, and anxiety (and its various substitutions) is the central symptom of all psychoneuroses.

The thesis of the presentation as I understand it is that 52 of the 100 patients presented a personality characterized by emotional immaturity, failure to grow up and anxiety. My experience is at variance with these observations, for I find a divergence of personality types with the several forms of psychoneurosis. If the neurotic personality can be delineated at all, it must conform more with the concept presented earlier this evening by Dr. Noyes. The neurotic personality is intermediary between one presenting neurotic symptoms and the normal, that is, one in which the neurotic symptoms are built into the character, awaiting precipitating causes for symptom formation. This description is less specific but probably more accurate.

Neuropsychiatrists are always in danger in designating patients as psychoneurotic because of the danger of overlooking coexisting somatic disease. One internist made a follow-up study of 100 neurotic patients and found that in many of them carcinoma, tuberculosis and other visceral disease developed. This study led to false conclusions, since all psychoneurotic persons sooner or later succumb to physical disease. There can be no doubt, on the one hand, that psychoneurotic persons have a predisposition to certain physical complications and, on the other, that the neurologist should not go overboard and ascribe definite visceral disease to psychogenic factors. Is ulcerative colitis a psychosomatic disease? I do not believe it, particularly when I see a piece of the affected gut. If we had what these patients with ulcerative colitis have, we should be more neurotic than they! The

appearance of physical disease in the psychoneurotic person does not mean, however, that he does not have symptoms of emotional origin.

DR. ROBERT A. MATTHEWS: This paper opens a point for discussion—namely, what cases should be classified under psychosomatic disorders and what cases should still be classified under psychoneurotic reaction types? There is confusion in this regard, and in line with our efforts to educate physicians in general practice and in other specialties, we in psychiatry should agree as to what is to be included under the term psychosomatic.

I wish to ask Dr. Flumerfelt why these persons remained dependent, why they failed to grow up emotionally. Was there anything in the past history which would account for their failure to go beyond an infantile stage?

DR. HOWARD P. ROME: Dr. Flumerfelt purposely did not attempt to classify these patients as having psychosomatic or somatopsychic disorders. He has excluded those whom the referring clinicians recognized as having overt psychoneuroses. The nosologic category of "psychosomatic" seems to be made on the basis of the patient's being referred with such a diagnosis by the other medical services. That of itself excludes psychiatric prejudice. Perhaps Dr. Flumerfelt can more clearly state the choice of patients as presented, since the objections raised center about this point.

DR. MAX ROSSMAN, Allentown, Pa.: Suppose one has a patient who fits into the personality type 0, who has had lower abdominal pain and who later has carcinoma of the colon; what does one call him?

DR. LOUIS H. TWYEFFORT: In this series of 100 cases which were classified according to physiologic symptoms, were the conclusions based on symptoms spontaneously expressed by the patients or on symptoms assented to in response to specific questioning?

Another point: Will not the eventual logical classification depend on the developmental age period at which a patient has shown the earliest symptoms of his psychosomatic disorder and the age period at which the still active conflicts first appeared? Should one not be able better to study these functional disorders as they occur in adults were one to study them as they initially occur in the child, such studies being intensively carried out from the psychologic, the physiologic and the laboratory point of view?

DR. BALDWIN L. KEYES: Dr. Noyes has beautifully explained the evolution of a personality in which a neurosis is likely to develop. In the study which Dr. Flumerfelt and I have made the most significant finding in a group of patients with neuroses seems to have been the personality noted in the majority. Interestingly, this personality type fits in well with the type Dr. Noyes describes as the one in which a neurosis is most likely to develop, so that from entirely different approaches Dr. Noyes and Dr. Flumerfelt and I seem to have reached the same conclusion.

To clarify the method of study made of this group of cases, it may be well to reemphasize that every effort has been made to avoid standard classifications and the problem has been studied by the accumulation of data, as far as possible without preconceived ideas for the use of these data but with the purpose of obtaining some estimate of factors most common to all.

The summaries seem to indicate that rather than any type of neurosis or any type of physical disturbance, the greatest common denominator is the personality type.

The relation of pain to neuroses, which has come up in the discussion, is a large subject and will require further study. In discussion, also, there has arisen some effort to determine whether the patients demonstrate somatopsychic or psychosomatic factors predominantly. This seems relatively unimportant in light of the present paper, in which an effort is being made to get away from classified descriptions and to understand more of the etiologic backgrounds on which neuroses develop.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

JAMES B. AYER, M.D., *Presiding*

Regular Meeting, Nov. 13, 1941

The Sign of Babinski in Macaca Mulatta. DR. FRANCIS M. FORSTER and DR. JAMES B. CAMPBELL.

Fulton and Keller reported the production of a positive Babinski sign by hemisection of the lower thoracic portion of the cord in Macaca mulatta. These authors also reported the presence of a normal plantar response following unilateral or bilateral ablation of area 4. Fulton and McCouch described a positive Babinski response following hemidecortication and removal of the thalamus and striatum.

In the present investigation the following experiments failed to produce a positive Babinski response in Macaca mulatta: (1) section of the lateral column of the cord; (2) bilateral ablation of areas 4 and 6; (3) bilateral ablation of areas 4, 6, 3, 1 and 2, and (4) section of the lateral column of the cord with ipsilateral ablation of areas 4 and 6 and the gyrus cinguli.

The following procedures resulted in a positive Babinski sign in Macaca mulatta: (1) bilateral ablation of areas 4 and 6 with subdural hematoma; (2) bilateral ablation of areas 4 and 6 and section of the corpus callosum, and (3) ligation of the anterior cerebral artery.

From these results, it is concluded that the Babinski sign can be elicited in Macaca mulatta by lesions of the cortex, that these lesions must be extensive and bilateral and that apparently no specific cortical area is responsible. From these deductions, it is obvious that the degree of encephalization in the macaque is greater than was previously considered, and this species, then, truly represents an intermediate stage between the lower mammalian form and the higher primates.

Twins, Brain Waves and Epilepsy. DR. W. G. LENNOX, E. L. GIBBS and DR. F. A. GIBBS.

Are the fluctuations which are registered in the electroencephalogram like the waves on the surface of the ocean, the manifestation of environmental forces of wind and current, or are they like the ocean tides, mainly influenced by gravitational, essential forces of the universe? To adopt another comparison, are they like a person's facial expression, which changes from moment to moment, a mirror of his many emotions, or are they like his features, which resemble the features of parents or grandparents and which change but little through the fortunes of the years? If the electroencephalograms of identical twins, which have the same heredity, prove to be indistinguishable and also the records of nonidentical twins, which have a different heredity, prove to be unlike, then the electrical pulsations of the brain represent a fundamental constitutional characteristic of the person. Close study might reveal correlations between these pulsations and inherited traits of personality or of mind. Again, disturbances of brain rhythm which were not the result of injuries to the brain could be used to trace heredity in certain nervous and mental diseases.

We have collected electrical records on 420 persons, either twins or near relatives of persons with cerebral dysrhythmia or both. Records for electrical analysis and psychometric studies were made, but the present paper deals only with the ink records. These records were inspected by one of us (E. L. G.) without knowledge of whether the twins were identical or not. Tracings were called identical if one record appeared to be a continuation of the other. Altogether, 70 sets of twins were studied, or 140 subjects. These 420 persons were divided into three groups:

1. Fifty-three sets of twins, "normal" in the sense of having no personal history of epilepsy or injury to the brain. Of the group of 41 sets of monozygotic twins,

electrical records were judged to be identical for 35, doubtful for 5 and definitely not identical for 1. Of the group of 5 sets of dizygotic twins of the same sex, the electroencephalograms were judged dissimilar for 4 and similar for 1. Of the group of 7 pairs of twins of opposite sex, the records were obviously dissimilar for all. In the whole group of 53 pairs of "normal" twins, the electrical test of similarity or dissimilarity agreed with their similarity or dissimilarity as judged by physical traits in 87 per cent, the correlation was doubtful in 9 per cent and there was negative correlation in 4 per cent. These results, therefore, indicate a high degree of correlation between similarity of brain wave records and similarity of those physical characteristics which denote single or double-egged twins. Newman states that heredity is 90 per cent responsible for fingerprints, 81 per cent for height, 78 per cent for weight and 68 per cent for intelligence. Although differing methods of analysis do not permit direct comparison of our figures with those of Newman, it would appear that electroencephalograms are as significant as weight or height in judging the identity of twins.

2. Seventeen pairs of twins, one or both of whom had a history of epilepsy or injury to the brain. Fifteen of these had a history of convulsive seizures in one or both members. These included 2 pairs of identical twins, both members of which had epilepsy and abnormal records. None of these 4 persons gave a history or showed neurologic evidence of injury to the brain. Of 7 pairs of identical twins, only 1 member of each was epileptic. Reports of instances of this sort in the literature have been a compelling argument against the all-important influence of heredity in epilepsy. In each of these 7 sets of twins, the normal as well as the epileptic member had pronounced dysrhythmia, although in most instances the disorder was not as pronounced or as localized as in the patient. In 5, or possibly in 6, of the 7 sets, the epileptic member had received an injury to the brain before the onset of seizures.

One set of similar twins illustrated what may be considered pure symptomatic epilepsy. One child had several convulsions and localized dysrhythmia as a result of an injury to the head. Her twin had a normal record, as did the injured child after six months. In another set of similar twins 1 member had hysterical seizures. Both members had normal and similar tracings. These 2 instances were the only ones in this series of 11 sets of identical twins in which the record of the unaffected member was normal.

There were 4 sets of dissimilar twins in which 1 member had epilepsy and the other did not. In 3 of these pairs the electroencephalogram of the normal member was normal.

3. Relatives of epileptic persons. Our present data are additional to those already reported (ARCH. NEUROL. & PSYCHIAT. **44**:1155 [Dec.] 1940). We have tracings of one or more members of the immediate family of 149 patients subject to seizures. Of the 280 relatives examined, the records of 52 per cent were definitely abnormal, those of 11 per cent were doubtful and those of 37 per cent were normal. The proportion of abnormalities was somewhat higher in females than in males and in mothers than in fathers, and was greater when both than when only one parent was examined, suggesting that the abnormal parent had died or avoided the test. In 81 families both parents of the patient were examined. Both records were considered normal in 8 per cent of the parents, one was doubtful and one normal in 12 per cent, one or both were definitely abnormal in 80 per cent and both were definitely abnormal in 27 per cent.

As a result of our experience, we believe that cerebral dysrhythmia which is not due to environmental factors is a hereditary trait and that this fact can be used in the determination of heredity and in the prevention of disorders of mind and of action which are associated with cerebral dysrhythmia. The case seems proved for epilepsy. Evidence concerning other conditions, such as behavior disorders, schizophrenia and alcoholism, requires investigation.

Epilepsy, the plant, is not inherited. A predisposition, the seed, is inherited. This is a trait which the electroencephalograph is instrumental in detecting.

Probably the great majority of patients who have traumatic or so-called symptomatic epilepsy had a preexisting hereditary dysrhythmia. In such a person an acquired injury or defect of the brain which is not consistently epileptogenic may act on an already present asymptomatic dysrhythmia and make it appear externally as epilepsy.

DISCUSSION

DR. ALFRED HAUPTMANN: Some years ago I had occasion to study identical twins for other purposes. I found several sets of identical twins with epilepsy. In 1 of these sets the onset of epilepsy occurred in the same year in both members. In another set the onset occurred three years apart. In a third set only one member had epileptic attacks. The other member did not show any epileptic signs or symptoms. In the second case, in which there was a difference of three years in the onset of the seizures, only one twin had idiopathic epilepsy; the other had his seizures after an injury to the brain. This raises the question whether post-traumatic epilepsy can develop only if the trauma concerns a brain with epileptic predisposition. My associates and I studied this problem in cases of post-traumatic epilepsy—this time, of course, without the use of electroencephalograms, but did not come to clearcut decisions. I should like to ask if you had occasion to examine family members of persons with post-traumatic epilepsy and if you found an epileptic predisposition in them.

DR. WILLIAM G. LENNOX: In studying our material we found that patients with so-called essential epilepsy have five times and patients with symptomatic epilepsy have three times as many relatives with epilepsy as nonepileptic persons. In our electroencephalographic work the identical twin with epilepsy had evidence of injury to the brain which the normal twin did not have and which apparently externalized his symptoms. In the case you mentioned, Dr. Hauptmann, there may have been injury to the brain in spite of the lack of signs, or possibly the nonepileptic member has developed epilepsy by now.

DR. KNOX H. FINLEY: I doubt if it is possible to overestimate the importance of this contribution to neuropsychiatry. I venture to say that this work is going to be confirmed as knowledge in the field of neuropsychiatry advances. This study is of interest to me particularly from the standpoint of abnormal tracings which my colleagues and I obtain from psychiatric patients, particularly those with major psychoses. In going over these records with Dr. Campbell, we were faced with the problem whether such abnormal patterns are of constitutional origin or are acquired secondary to some environmental factor or trauma to the head. In a few instances we were fortunate enough to obtain records on relatives of these patients, who likewise had atypical or abnormal electroencephalograms, a finding which suggests that the abnormal pattern of the patient was of constitutional origin. Such instances are in line with the studies presented by the authors this evening. The study makes it clear that in considering the cause or origin of abnormal patterns one must consider heredity or a constitutional factor, as well as factors occurring after birth.

DR. ROBERT S. SCHWAB: Have the authors examined other things, such as the myographic pattern, the electrocardiogram and the respiratory pattern? Is the response of these twins to anticonvulsant drugs the same as that of persons with ordinary epilepsy?

DR. WILLIAM G. LENNOX: We have not made the other tests which Dr. Schwab mentions. We gave dilantin to one of the twins who had seizures and intended to use the other twin as a "normal control," but, unfortunately, she began to have convulsions and had to be given the medicine too.

DR. DEREK DENNY-BROWN: I have greatly enjoyed the contribution of Dr. Lennox and his associates. An identical twin is surely the perfect control for constitutional factors in the electroencephalogram. I note that the small percentage of identical twins with dissimilar electroencephalograms approaches the percentage

with dissimilar fingerprints. Is it possible that in this group the criteria of uniovular origin are fallacious and that in uniovular twins there is complete identity?

I should like to ask what Dr. Lennox can tell of the type of head injury which seemed especially to provoke epilepsy in predisposed persons. I ask this with 2 patients in mind: One was a man who suffered a concussion while boxing. The next day he had an epileptic attack and from that time had four or five attacks a day. A fortnight later he had a grossly disordered interval electroencephalogram, and the attack showed the characteristic wave and spike pattern which I take it Dr. Lennox would hold to be that of constitutional epilepsy. The other patient had a minor injury. He was repairing a telegraph wire and had the usual strap contrivance for climbing poles. The strap broke and the man fell on soft turf. He did not injure his head directly and did not lose consciousness; an hour later, when telling of his experience, he had a major convulsion. He, too, began to have a series of attacks at short intervals. His electroencephalogram was grossly abnormal when taken about ten days after the injury. There was no history of family or constitutional liability. It is difficult to believe there was any damage to the brain. I wonder whether the epilepsy produced by cerebral scars is not, in fact, very different from the epilepsy provoked in a susceptible person by some sort of trauma.

Dr. William G. Lennox: I agree with Dr. Denny-Brown that the usual criteria for judging identicality, even finger ridges or a single placenta, are not 100 per cent dependable. Twins are never completely identical, and some "identical" twins are more alike than others. However, we blame the electroencephalogram, and not our physical criteria, for failure to agree in the 4 per cent of cases. As to antecedent dysrhythmia in a person with traumatic epilepsy, this suggestion is strengthened by the fact that the proportion of persons with injury to the brain who later have epilepsy is no greater than the proportion of the population with dysrhythmia. In our series of twins, the epileptic twin had had an injury either at birth or early in life. Epilepsy beginning in this period carries a larger hereditary factor than epilepsy beginning in adult life. The 3 a second alternate wave and spike formation of petit mal is not often seen in traumatic epilepsy. However, in 1 of our sets of twins, the child who had jacksonian epilepsy dating from birth also had electrical petit mal.

Dr. Frederic A. Gibbs: Dr. Denny-Brown has referred to the occurrence of the petit mal type of wave and spike discharges in a case of postconcussion stupor. Dr. Denis Williams and I have been corresponding on this subject. I believe the wave and spike formation of which Dr. Denny-Brown speaks is the 2 per second type, which we call a "petit mal variant" or a "slow wave and spike." We have never seen this formation accompanying a clinically evident petit mal seizure. It is relatively insensitive to inhalation of carbon dioxide and to changes in blood sugar and should, we believe, be differentiated from the true petit mal type of discharge. This formation and diphasic spikes are commonly seen in persons with a history of gross injury to the brain.

Of over 100 persons with post-traumatic epilepsy, clearly defined 3 per second wave and spike formations were shown by only 3. Among a little over 1,000 persons in our control series, 6 (approximately 0.6 per cent) had such discharges. On the basis of these figures it would appear, as Dr. Lennox has stated, that trauma is a negligible factor in the origin of true petit mal. However, in 2 of our 3 patients with post-traumatic epilepsy who had 3 per second wave and spike discharges, the discharge was definitely localized to the region of a depressed fracture. So localized a reaction suggests that the injury bore a causal relation to the discharge in these 2 patients.

Dr. Henry R. Viets: I want to be sure all have this idea correctly in mind. Is it true that the wave and spike formation of petit mal is never thought to be a late manifestation of trauma to the brain? It seems to me this is a very important point.

DR. FREDERIC A. GIBBS: In electroencephalography, as in many other fields, results must be stated in terms of probabilities. It is rarely possible to use such a strong word as "never." I believe that in this instance there is no need to exclude the possibility that trauma can produce the 3 per second wave and spike formation of petit mal in a previously normal brain. It should be recognized, however, that trauma is a relatively insignificant factor in petit mal epilepsy and that a constitutional predisposition is of paramount importance.

DR. WILLIAM G. LENNOX: On clinical grounds, without the electroencephalographic evidence, I believe that petit mal is more clearly an essential feature of epilepsy than grand mal. Petit mal is more frequently observed in females than in males. It is more frequently associated with adolescence than with injury to the brain.

Muscular Shortening and Dystrophy: A Heredofamilial Disease. DR. ALFRED HAUPTMANN and DR. S. J. THANNHAUSER.

This paper was published in full in the October 1941 issue of the ARCHIVES, page 654.

DISCUSSION

DR. JAMES B. AYER: Was there not a biopsy?

DR. ALFRED HAUPTMANN: No, there was no biopsy.

DR. JAMES B. AYER: The variations in dystrophy are very great, and this paper adds one more to the group. The disease is not very progressive, is it? Your filling station man did not know he had anything the matter with him.

DR. ALFRED HAUPTMANN: The disease began in childhood and progressed to a certain degree, but very slowly.

DR. JAMES B. AYER: Is not there a possibility of confusing platybasia with this shortness of the neck. Certainly, there was no evidence of platybasia in the roentgenogram?

DR. ALEXANDRA ADLER: I cannot understand the concept of the shortness of muscles. I thought that if a muscle was too short it could easily be stretched, unless a joint resisted it. A loose joint can be overstretched a great deal. Why cannot these muscles be stretched? What is the underlying pathologic condition? Could it be an increase in tonus? I wonder whether one could not find out more by electromyograms.

DR. ALFRED HAUPTMANN: If a muscle is too short it might be impossible to extend the arm entirely. You can stretch a muscle only to a certain degree.